

Overview of the Development of the Human Brain and Spinal Cord

Hans J. ten Donkelaar and Ton van der Vliet

1.1 Introduction

The development of the human brain and spinal cord may be divided into several phases, each of which is characterized by particular developmental disorders (Volpe 1987; van der Knaap and Valk 1988; Aicardi 1992; Table 1.3). After implantation, formation and separation of the germ layers occur, followed by dorsal and ventral induction phases, and phases of neurogenesis, migration, organization and myelination. With the transvaginal ultrasound technique a detailed description of the living embryo has become possible. Fetal development of the brain can now be studied in detail from about the beginning of the second half of pregnancy (Garel 2004). In recent years, much progress has been made in elucidating the mechanisms by which the CNS develops, and also in our understanding of its major developmental disorders, such as neural tube defects, holoprosencephaly, microcephaly and neuronal migration disorders. Molecular genetic data, that explain programming of development aetiologically, can now be incorporated (Sarnat 2000; Barkovich et al. 2001). In this chapter an overview is presented of (1) major stages in the development of the human CNS, (2) the first 3 weeks of development, (3) neurulation, (4) pattern formation, (5) early development of the brain, (6) fetal development of the brain, (7) the development of the blood supply of the brain, and (8) the development of major fibre tracts including the development of myelination. Mechanisms of development are discussed in Chap. 2, and an overview of the causes of developmental malformations and their molecular genetic basis is presented in Chap. 3. In the second, specialized part of this book the development of the CNS and its disorders are discussed in more detail.

1.2 Major Stages in the Development of the Human Brain and Spinal Cord

The **embryonic period** in man, i.e. the first 8 weeks of development, can be divided into 23 stages, the **Carnegie stages** (O'Rahilly and Müller 1987), originally described as developmental horizons (XI–XXIII) by Streeter (1951), and completed by Heuser and Corner (1957; developmental horizon X) and O'Rahilly (1973; developmental stages 1–9). Impor-

tant contributions to the description of human embryos were also made by Nishimura et al. (1977) and Jirásek (1983, 2001, 2004). Examples of human embryos are shown in Figs. 1.1 and 1.2. In the embryonic period, **postfertilization** or **postconceptional age** is estimated by assigning an embryo to a developmental stage using a table of norms, going back to the first *Normentafeln* by Keibel and Elze (1908). The term **gestational age** is commonly used in clinical practice, beginning with the first day of the last menstrual period. Usually, the number of **menstrual** or **gestational weeks** exceeds the number of postfertilization weeks by 2. During week 1 (stages 2–4) the blastocyst is formed, during week 2 (stages 5 and 6) implantation occurs and the primitive streak is formed, followed by the formation of the notochordal process and the beginning of neurulation (stages 7–10). Somites first appear at stage 9. The neural folds begin to fuse at stage 10, and the rostral and caudal neuropores close at stages 11 and 12, respectively. Gradually, the pharyngeal bars, the optic and otic vesicles and the limb buds appear. The main external and internal features of human embryos are summarized in Table 1.1. The first four embryonic weeks are also described as the period of *blastogenesis*, and the fifth to eighth weeks as the period of *organogenesis* (Opitz 1993; Opitz et al. 1997). The **fetal period** cannot be divided into a series of morphologically defined stages. It is the period of *phenogenesis* (Opitz 1993; Opitz et al. 1997). In the clinical literature a subdivision of the prenatal period into three trimesters of 13 weeks each is commonly used. At the junction of trimesters 1 and 2, the fetus of about 90 days has a greatest length of 90 mm, whereas at the junction of trimesters 2 and 3, the fetus is about 250 mm in length and weighs approximately 1,000 g (O'Rahilly and Müller 2001; Table 1.2). The newborn brain weighs 300–400 g at full term. Male brains weigh slightly more than those of females but, in either case, the brain constitutes 10% of the body weight (Crelin 1973).

The brain and spinal cord arise from an area of the ectoderm known as the neural plate. The folding of the neural plate, leading to successively the neural groove and the neural tube, is called primary neurulation. The caudal part of the neural tube does not arise by fusion of the neural folds but develops from the so-called caudal eminence. This process is called secondary neurulation (Chap. 4). Before and after the

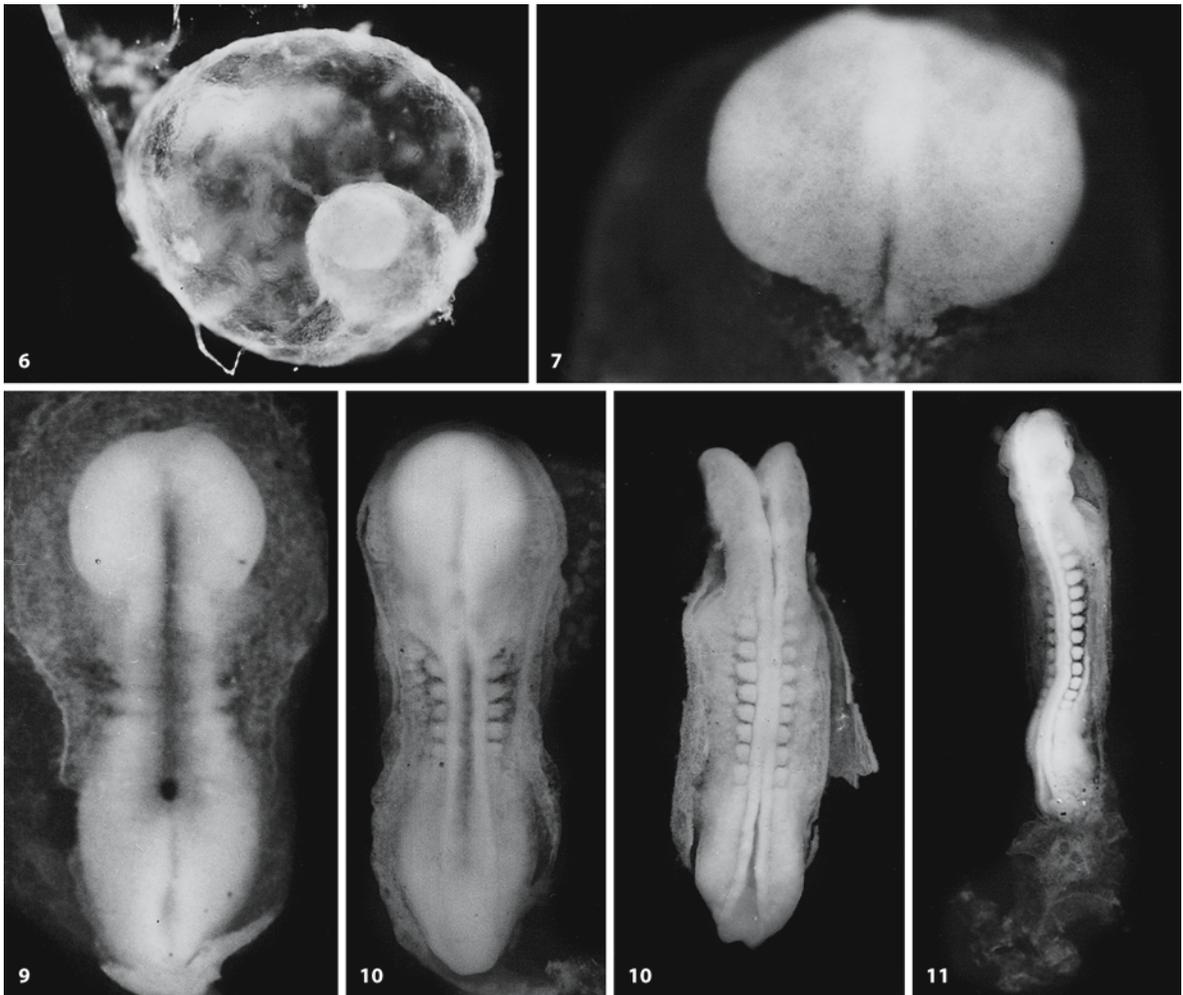


Fig. 1.1 Dorsal views of staged early human embryos (Carnegie stages 6, 7, 9–11; from the Kyoto Collection of Human Embryos; kindly provided by Kohei Shiota)

surface ectoderm of the two sides fuses, the fusing neuroectodermal cells of the neural folds give off the neural crest cells. The neural crest is a transient structure and gives rise to the spinal and cranial ganglia. Moreover, the whole viscerocranium and part of the neurocranium are formed from the neural crest (Le Douarin and Kalcheim 1999; Wilkie and Morriss-Kay 2001; Chap. 5).

The embryonic period includes three in time overlapping phases: formation and separation of the germ layers, dorsal and ventral induction phases (Table 1.3). During the first phase, the neural plate is formed. In the **dorsal induction phase**, the neural tube is formed and closed, and the three primary divisions or neuromeres of the brain (the prosencephalon, mesencephalon and rhombencephalon) appear. In the **ventral induction phase** (*telencephalization*), the cerebral hemispheres, the eye vesicles, the olfactory bulbs and tracts, the pituitary gland and

part of the face are formed. In the sixth week of development strong proliferation of the ventral walls of the telencephalic vesicles gives rise to the ganglionic or ventricular eminences. These elevations do not only form the basal ganglia but, in addition, give rise to many neurons that migrate tangentially to the cerebral cortex. **Neurogenesis** starts in the spinal cord and the brain stem. Neurogenesis in the cerebellum and the cerebral cortex occurs largely in the fetal period. In man, the **fetal period** extends from the ninth week of development to the time of birth. With regard to the prenatal ontogenesis of the cerebral cortex, Marín-Padilla (1990) suggested dividing this long developmental period into two separate ones: (1) the **fetal period proper** (9–24 gestational weeks), characterized by the formation of the cortical plate; and (2) the **perinatal period**, extending from the 24th week of gestation to the time of birth. This period is characterized by neuronal maturation. The separation be-

Table 1.1 Developmental stages and features of human embryos (after O’Rahilly; Müller 1987, 2001)

Carnegie stages	Length (mm)	Age (days)	External features	Internal features (with emphasis on the nervous system)
1		1	Fertilization	
2		2–3	From 2 to about 16 cells	
3		4–5	Free blastocyst	Inner cell mass and trophoblast
4		6	Attaching blastocyst	Cytotrophoblast and syncytiotrophoblast distinguishable
5	0.1–0.2	7–12	Implantation; embryonic disc circular	Amniotic cavity; primary yolk sac; extra-embryonic mesoderm
6	0.2	17	Embryonic disc elongated	Chorionic villi; primitive streak and node; prechordal plate appears; secondary yolk sac
7	0.4	19	Embryonic disc oval	Notochordal process visible; haematopoiesis starts
8	1.0–1.5	23	Primitive pit appears; neural folds may begin to form	Notochordal and neurenteric canals detectable
9	1.5–2.5	25	First somites appear; mesencephalic flexure begins; otic disc forms	Neural groove evident; 3 major subdivisions of brain distinguishable; heart begins to develop
10	2–3.5	28	Neural folds begin to fuse; otic pit develops; 4–12 somites; pharyngeal arches 1 and 2 visible	Optic primordium begins to develop; cardiac loop appears; intermediate mesoderm
11	2.5–4.5	29	Rostral neuropore closes; 13–20 somites	Optic vesicles develop
12	3–5	30	Caudal neuropore closes; 21–29 somites; 4 pharyngeal arches visible; upper limb buds appearing	Secondary neurulation starts
13	4–6	32	Otic vesicle closed; lens disc not yet indented; 30 or more somites; 4 limb buds visible	Retinal and lens discs develop; primordium of cerebellum
14	5–7	33	Lens pit appears; upper limb buds elongated	Future cerebral hemispheres; pontine flexure; optic cup develops; adenohipophysial pouch defined
15	7–9	36	Lens pit closed; nasal pit appearing; hand plate forming	Future cerebral hemispheres become defined; retinal pigment visible
16	8–11	38	Retinal pigment visible; nasal sacs face ventrally; auricular hillocks beginning; foot plate appears	Epiphysis cerebri develops; neurohypophysial evagination; olfactory tubercle
17	11–14	41	Head relatively larger; trunk straighter; auricular hillocks distinct; finger rays	Internal and external cerebellar swellings; chondrification begins in humerus, radius and some vertebral centra
18	13–17	44	Body more cuboidal; elbow region and toe rays appearing	Oronasal membrane develops; 1–3 semicircular ducts in internal ear
19	16–18	46	Trunk elongating and straightening	Olfactory bulb develops; cartilaginous otic capsule; choroid plexus of fourth ventricle
20	18–22	49	Upper limbs longer and bent at elbows	Optic fibres reach optic chiasm; choroid plexus of lateral ventricle
21	22–24	51	Fingers longer; hands approach each other, feet likewise	Cortical plate becomes visible; optic tract and lateral geniculate body
22	23–28	53	Eyelids and external ear more developed	Olfactory tract; internal capsule; adenohipophysial stalk incomplete
23	27–31	56	Head more rounded; limbs longer and more developed	Insula indented; caudate nucleus and putamen recognizable; humerus presents all cartilaginous stages

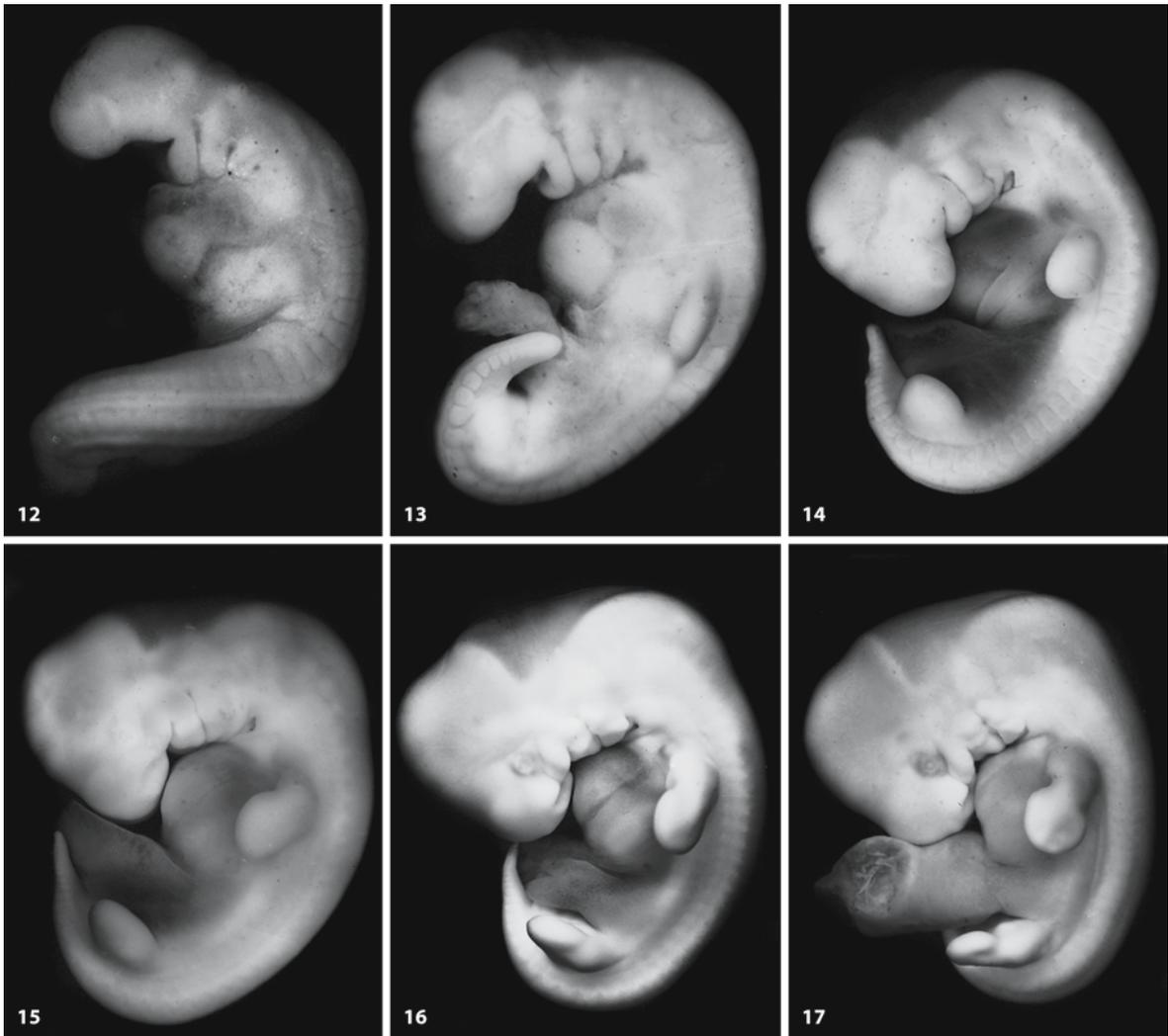


Fig. 1.2 Lateral views of staged human embryos (Carnegie stages 12–23; from the Kyoto Collection of Human Embryos; kindly provided by Kohei Shiota)

tween these two periods at the 24th week of gestation is somewhat arbitrary but may be clinically relevant. The 24th week of gestation approximates roughly the lower limit for possible survival of the prematurely born infant. Disorders of migration are more likely to occur in the fetal period, whereas abnormalities affecting the architectonic organization of the cerebral cortex are more likely to occur in the perinatal period (Chap. 10).

Each of the developmental phases of the brain is characterized by particular **developmental disorders** (Table 1.3). During the separation of the germ layers, enterogenous cysts and fistulae may occur. In the dorsal induction phase, neural tube defects (Chap. 4)

occur. Developmental disorders in the ventral induction phase, in which the prosencephalon is normally divided into the diencephalon and the two cerebral hemispheres, are characterized by a single, incompletely divided forebrain (holoprosencephaly; Chap. 9). This very heterogeneous disorder may be due to disorders of ventralization of the neural tube (Sarnat 2000) such as underexpression of the strong ventralizing gene *Sonic hedgehog* (*SHH*). During neurogenesis of the forebrain, malformations due to abnormal neuronal proliferation or apoptosis may occur, leading to microcephaly or megalcephaly. During the migration of the cortical neurons, malformations due to abnormal neuronal migration may



Fig. 1.2 (Continued)

appear, varying from classic lissencephaly ('smooth brain'), several types of neuronal heterotopia, polymicrogyria to minor cortical dysplasias. For many of these malformations, disorders of secretory molecules and genes that mediate migration have been found (Chap. 10). Many of these malformations are characterized by the presence of mental retardation and epilepsy. Cerebellar disorders are more difficult to fit into this scheme. The Dandy-Walker malformation is thought to arise late in the embryonic period, whereas cerebellar hypoplasia presumably occurs in the fetal period. These malformations are discussed in Chap. 8.

1.3 The First 3 Weeks of Development

During the first 3 weeks of development, the three germ layers (ectoderm, mesoderm and endoderm), the basis of the various organs and systems of the body, are established. During the first week of development (stages 2–4), the embryo develops from a solid mass of totipotent cells or blastomeres (the **morula**) into the blastocyst. This occurs when 16–32 cells are present. The **blastocyst** is composed of an inner cell mass or **embryoblast**, giving rise to the embryo, and the **trophoblast**, the peripherally situated cells, surrounding the blastocystic cavity and forming the developmental adnexa (Fig. 1.3). Embryoblast cells

Table 1.2 Criteria for estimating age during the fetal period (after Moore et al. 2000)

Age (post-conceptional weeks)	Average crown–rump length (mm)	Average foot length (mm)	Average weight (g)	Main external characteristics
Previable fetuses				
9	50	7	8	Eyes closing or closed; head large and more rounded; external genital not distinguishable as male or female; intestines in proximal part of umbilical cord; low-set ears
10	61	9	14	Intestines returned to abdomen; early fingernail development
12	87	14	45	Sex distinguishable externally; well-defined neck
14	120	20	110	Head erect; eyes face anteriorly; ears close to their definitive position; lower limbs well-developed; early toenail development
16	140	27	200	External ears stand out from head
18	160	33	320	Vernix caseosa covers skin; quickening felt by mother
20	190	39	460	Head and body hair (lanugo) visible
Viable fetuses				
22	210	45	630	Skin wrinkled, translucent, pink to red
24	230	50	820	Fingernails present; lean body
26	250	55	1,000	Eyes partially open; eyelashes present
28	270	59	1,300	Eyes wide open; good head of hair may be present; skin slightly wrinkled
30	280	63	1,700	Toenails present; body filling out; testes descending
32	300	68	2,100	Fingernails reach finger tips; skin pink and smooth
36	340	79	2,900	Body usually plump; lanugo hairs almost absent; toenails reach toe tips; flexed limbs; firm grasp
38	360	83	3,400	Prominent chest; breasts protrude; testes in scrotum or palpable in inguinal canals; fingernails extend beyond finger tips

adjacent to this cavity form a new layer of flat cells, the **hypoblast**. This cell layer covers the blastocystic cavity from inside what is now called the **primitive umbilical vesicle** or **yolk sac**. The rest of the inner cell mass remains relatively undifferentiated and is known as the **epiblast**. Duplication of the inner cell mass is probably the basis for most cases of monozygotic twinning. Possibly, such divisions arise during ‘hatching’, the emergence of the blastocyst from the zona pellucida (O’Rahilly and Müller 2001). At approximately 6 days (stage 4b), the blastocyst becomes attached to the endometrium of the uterus.

1.3.1 Implantation

The second week is characterized by **implantation** (stage 5) and the formation of the primitive streak (stage 6). The trophoblast differentiates into the **cytotrophoblast** and the more peripherally situated **syncytiotrophoblast** that invades the endometrium. Blood-filled spaces, the **lacunae**, soon develop within

the syncytiotrophoblast and communicate with endometrial vessels, laying the basis for the placental circulation. Between the epiblast and the cytotrophoblast, the **amniotic cavity** appears. The embryonic disc is now known as the **bilaminar embryo**. Only the cylindrical epiblast cells adjacent to the hypoblast form the embryo. The remaining flattened epithelial cells participate in the formation of the amnion (Fig. 1.3). The amniotic cavity is bounded ventrally by the epiblast and dorsally by a layer of amniotic ectoderm.

1.3.2 Gastrulation

During stage 6, in the slightly elongated embryonic disc caudally situated cells of the epiblast migrate ventralwards along the median plane, and form the **primitive streak** (Fig. 1.4). It probably appears between days 12 and 17 (Jirásek 1983, 2001; Moore et al. 2000; O’Rahilly and Müller 2001). The rostral, usually distinct part of the primitive streak is known as the

Table 1.3 Major stages of human CNS development (based on Aicardi 1992)

Stage	Time of occurrence (weeks)	Major morphological events in brain	Main corresponding disorders
Embryonic period			
Formation and separation of germ layers	2	Neural plate	Enterogenous cysts and fistulas; split notochord syndrome
Dorsal induction: primary neurulation	3–4	Neural tube, neural crest and derivatives; closure of rostral and caudal neuropores; paired alar plates	Anencephaly, encephalocele, myeloschisis; myelomeningocele, Chiari malformations
Ventral induction: telencephalization	4–6	Development of forebrain and face; formation of cerebral vesicles; optic and olfactory placodes; rhombic lips appear; 'fusion' of cerebellar plates	Holoprosencephaly; Dandy–Walker malformation; craniosynostosis
Fetal period			
Neuronal and glial proliferation	6–16	Cellular proliferation in ventricular and subventricular zones; early differentiation of neuroblasts and glioblasts; cellular death (apoptosis); migration of Purkinje cells and external granular layer in cerebellum	Microcephaly, megalencephaly
Migration	12–24	Migration of cortical neurons; formation of corpus callosum	Neuronal migration disorders (lissencephalies, polymicrogyria, schizencephaly, heterotopia)
Perinatal period			
Organization	24 to postnatal	Late migration; organization and maturation of cerebral cortex; synaptogenesis; formation of internal granular layer in cerebellum	Minor cortical dysplasias
Myelination	24 to 2 years postnatally		Myelination disorders, destructive lesions (secondarily acquired injury of normally formed structures)

primitive node of Hensen. The primitive streak is a way of entrance whereby cells invaginate, proliferate and migrate to subsequently form the extra-embryonic mesoderm, the endoderm and the intra-embryonic mesoderm. Remnants of the primitive streak may give rise to *sacroccygeal teratomas* (Chap. 6). The **endoderm** replaces the hypoblast. The remaining part of the epiblast is the **ectoderm**. For this process the term **gastrulation** is frequently used. Originally, the term referred to the invagination of a monolayered blastula to form a bilayered gastrula, containing an endoderm-lined archenteron as found in amphibians (Chap. 2). Nowadays, the term gastrulation is more generally used to delimit the phase of development from the end of cleavage until the formation of an embryo possessing a defined axial structure (Collins and Billett 1995).

Rostral to the primitive streak and node, the endoderm appears thicker and is called the **prechordal plate**. Caudally, the epiblast is closely related to the endoderm, giving rise to the **cloacal membrane** (Fig. 1.4). The primitive streak is the first clear-cut in-

dication of bilaterality, so the embryo now, apart from rostral and caudal ends, also has right and left sides. Genetic mutations expressed in the primitive streak may lead to duplication of the neural tube (Chap. 6) or its partial or complete agenesis (Sarnat 2000).

The **extra-embryonic mesoderm** soon covers the trophoblast, the amniotic ectoderm and the yolk sac (Fig. 1.3). Extra-embryonic mesoderm at the caudal part of the embryo forms the **connecting** or **umbilical stalk** that anchors the embryo to the **chorion**. The chorion is composed of the trophoblast and the covering extra-embryonic mesoderm. Hypoblast cells and the covering extra-embryonic mesoderm form the wall of the yolk sac, whereas the amniotic epithelium and its mesodermal layer form the **amnion**. The **secondary umbilical vesicle** or **yolk sac** develops from the primary one, probably by collapse and disintegration of the latter (Luckett 1978). The yolk sac is involved in active and passive transport to the embryo, and is possibly associated with the relationship between metabolic disorders such as diabetes melli-

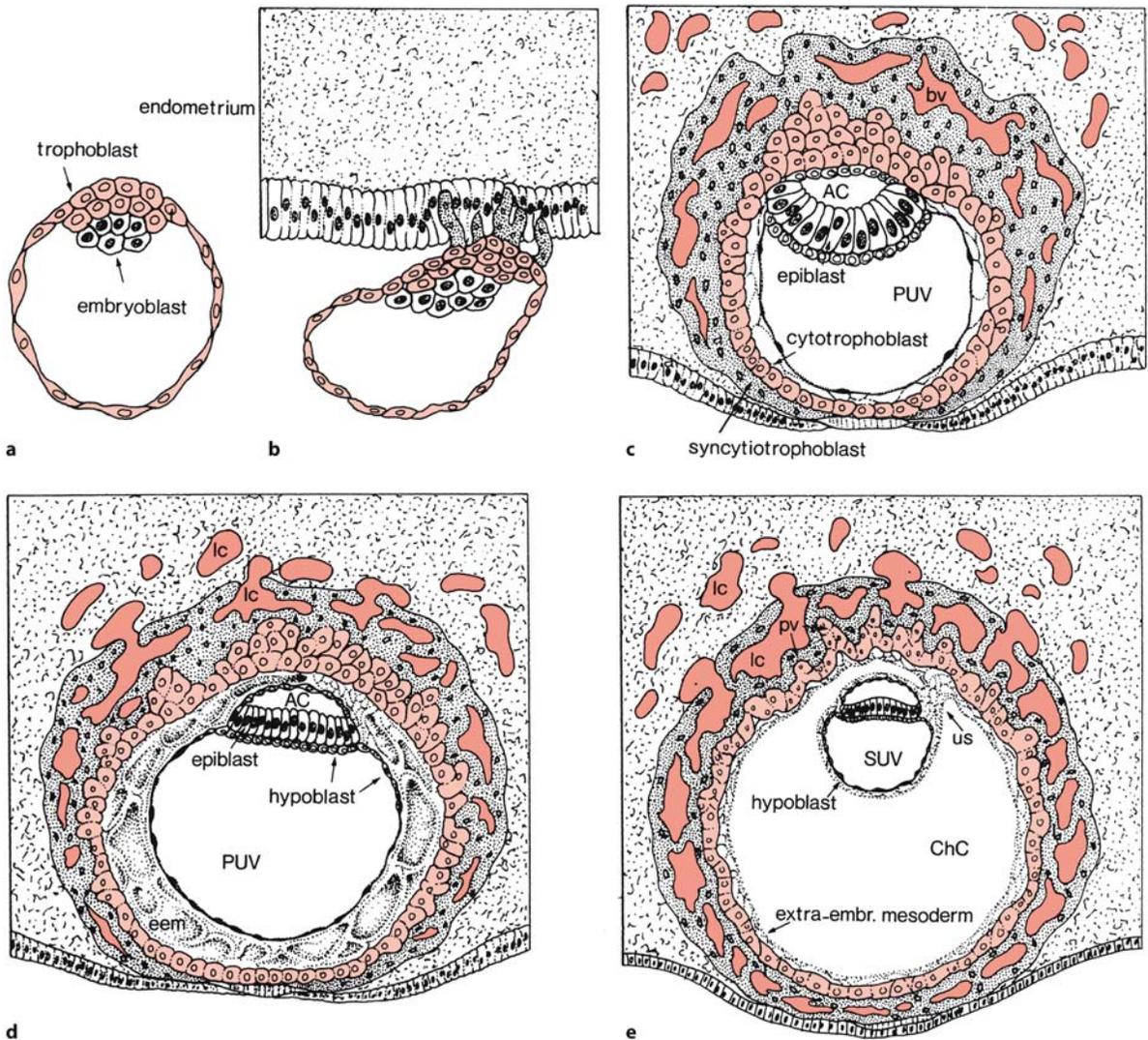


Fig. 1.3 Implantation and the formation of the bilaminar embryo: **a** 107-cell blastocyst; **b–e** blastocysts of approximately 4.5, 9, 12 and 13 days, respectively. The trophoblast and the cytotrophoblast are indicated in *light red*, the syncytiotrophoblast is *stippled* and maternal blood in lacunae is shown in

red. AC amniotic cavity, ChC chorionic cavity, eem extra-embryonic mesoderm, lc lacuna, PUV primary umbilical vesicle, pv primary villi, SUV secondary umbilical vesicle (yolk sac), us umbilical stalk. (After Langman 1963)

tus and congenital malformations (O’Rahilly and Müller 2001). The chorion encloses the **chorionic cavity**, in which the embryonic disc, now a **trilaminar embryo**, is located.

During the third and the fourth weeks, the somites, the heart, the neural folds, the three major divisions of the brain, the neural crest and the beginnings of the internal ear and the eye develop. At approximately 19 days (stage 7), rostral to the primitive streak, a prolongation below the ectoderm, the **notochordal process**, arises from the primitive node, and extends rostrally as far as the prechordal plate (Fig. 1.4). The floor of the notochordal process breaks down at stage 8, giving rise to the notochordal plate.

The embryonic disc is now broader rostrally, and a shallow neural groove appears, which is the first morphological indication of the nervous system (O’Rahilly 1973; O’Rahilly and Gardner 1979; O’Rahilly and Müller 1981; Jirásek 2001, 2004). The primitive node may be followed by a **primitive pit**, which extends into the notochordal process as the **notochordal canal** (O’Rahilly 1973). The channel becomes intercalated in the endoderm, and its floor begins to disintegrate at once, allowing temporary communication between the amniotic cavity and the umbilical vesicle. The remnant of the notochordal canal at the level of the primitive pit is known as the **neurenteric canal** (Fig. 1.5a). It may be involved in

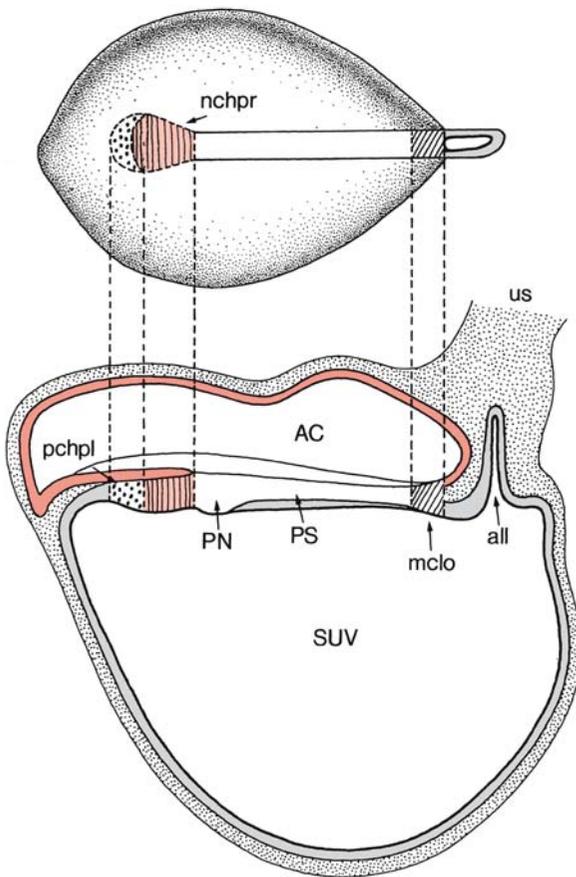


Fig. 1.4 Dorsal (top) and medial (bottom) views of a stage 7 embryo. The ectoderm is indicated in red, the notochordal process (*nchpr*) in light red and the endoderm in grey. *AC* amniotic cavity, *all* allantois, *mclo* membrana cloacalis, *pchpl* prechordal plate, *PN* primitive node, *PS* primitive streak, *SUV* secondary umbilical vesicle (yolk sac), *us* umbilical stalk. (After O’Rahilly 1973)

the pathogenesis of *enterogenous cysts* (Chap. 6). The **prechordal plate** is wider than the notochordal process, and is in close contact with the floor of the future forebrain. The prechordal plate is derived from the prechordal mesendoderm (de Souza and Niehrs 2000) and it is essential for the induction of the forebrain. The prechordal plate is usually defined as mesendodermal tissue underlying the medial aspect of the anterior neural plate just anterior to the rostral end of the notochord.

1.3.3 Folding of the Embryo

At approximately 25 days (stage 9), **folding** of the embryo becomes evident. Rostral or cephalic and caudal folds overlie the beginning foregut and hindgut, re-

spectively (Fig. 1.5). Caudal to the cloacal membrane, the allantois arises as a dorsal diverticle of the umbilical vesicle. On each side the mesoderm is arranged into three components (Fig. 1.5 e): (1) a longitudinal, **paraxial band** adjacent to the notochord, forming the somites; (2) **intermediate mesoderm**, giving rise to the urogenital system; and (3) a **lateral plate**, giving rise to two layers covering the body wall and the viscera, respectively. The first layer is known as the **somatopleure**, the other as the **splanchnopleure**. In the Anglo-Saxon literature, however, the terms somatopleure and splanchnopleure include the covering ectoderm and endoderm, respectively (O’Rahilly and Müller 2001). The space between the somatopleure and the splanchnopleure is the **coelom**. At first it is found outside the embryo (the *extra-embryonic coelom*), later also within the embryo. This is the *intra-embryonic coelom* or body cavity, which develops in the lateral plate mesoderm (Fig. 1.5 e, f).

Somites arise at stage 9 in longitudinal rows on each side of the neural groove. The first four pairs of somites belong to the occipital region. Within the next 10 days subsequently 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and some 3–6 coccygeal somites are formed, but they are never visible together at one stage of development. Each somite divides into a ventromedial **sclerotome**, participating in the formation of the vertebral column (Chap. 6), and a dorsolateral **dermamyotome** that forms a myotome and the overlying dermis (**dermatome**). Each **myotome** divides into two parts: (1) a dorsal *epimere*, giving rise to the erector spinae, and (2) a ventral *hypomere*, from which the ventral vertebral muscles (*epaxial* muscles), the muscles of the lateral and ventral body wall (*hypaxial* muscles) and the muscles of the extremities arise. The derivatives of the epimeres become innervated by the dorsal rami of the spinal nerves, those of the hypomeres by the ventral rami (Chap. 6).

The primitive streak becomes confined to a region known as the **caudal eminence**, or end-bud, which gives rise to the hindgut, adjacent notochord and somites, and the most caudal part of the spinal cord (O’Rahilly and Müller 2001). Malformations in this region may lead to the still poorly understood **caudal regression syndrome** that is discussed in Chap. 4. Rostrally, the ectoderm and the endoderm come together as the **oropharyngeal membrane**, which temporarily separates the gut from the amniotic cavity. Pharyngeal arches, clefts and pouches become visible. The **pharyngeal arches** are separated by the **pharyngeal clefts**, and appear ventrolaterally on the head and neck between 4 and 5 weeks. Four pairs are visible at stage 13 (Fig. 1.2). More caudally, no clear-cut arrangement is found, but it is customary to distinguish a fifth and a sixth arch. The externally situated clefts have internal counterparts, the **pharyngeal pouches**. The development of the pharyngeal arches

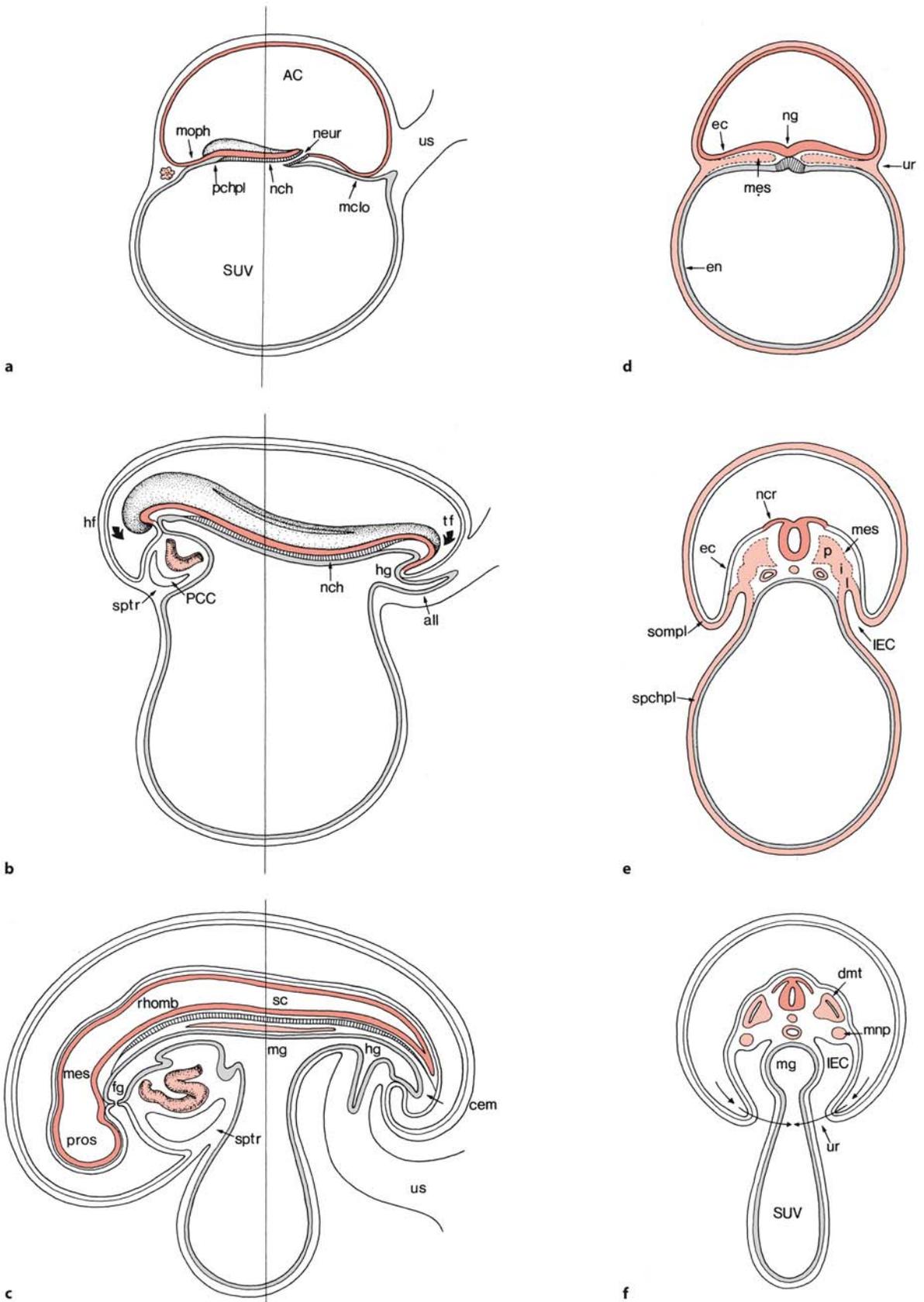


Fig. 1.5

Fig. 1.5 The folding of the embryo: **a, d** Carnegie stage 8; **b, e** Carnegie stage 10; **c, f** Carnegie stage 11/12. The ectoderm (*ec*) and its derivatives are indicated in red, derivatives of the mesoderm (*mes*) in light red and the endoderm (*en*) in grey. *AC* amniotic cavity, *all* allantois, *cem* caudal eminence, *dmt* dermamyotome, *fg* foregut, *hf* head fold, *hg* hindgut, *i* intermediate mesoderm, *IEC* intra-embryonic coelom, *l* lateral plate of mesoderm, *mclo* membrana cloacalis, *mes* mesencephalon, *mg* midgut, *mnp* mesonephros, *moph* membrana oropharyngealis, *nch* notochord, *ncr* neural crest, *neur* neurenteric canal, *ng* neural groove, *p* paraxial mesoderm, *PCC* pericardiac cavity, *pchpl* prechordal plate, *pros* prosencephalon, *rhomb* rhombencephalon, *sc* spinal cord, *sompl* somatopleure, *spchpl* splanchnopleure, *sptr* septum transversum, *SUV* secondary umbilical vesicle (yolk sac), *tf* tail fold, *ur* umbilical ring, *us* umbilical stalk. (After Streeter 1951; Hamilton and Mossman 1972)

is closely related to that of the rhombomeres and the neural crest, and is controlled by *Hox* genes (Favier and Dollé 1997; Rijli et al. 1998). Each pharyngeal arch is characterized by a unique combination of *Hox* genes. Rostral to the somites, the paraxial mesoderm forms the **somitomeres** from which the external eye musculature and the muscles of the pharyngeal bars arise (Noden 1991). These aspects and developmental disorders of the pharyngeal arches are discussed in

Chap. 5. The major sensory organs of the head develop from the interactions of the neural tube with a series of epidermal thickenings called the **cranial ectodermal placodes**. The olfactory placode forms the olfactory epithelium, the trigeminal placode the trigeminal ganglion, the otic placode or disc forms the inner ear, and the epibranchial placodes the distal ganglia of the VIIth, IXth and Xth nerves. The lens placode forms the lens and induces the overlying ectoderm to form the transparent cornea.

1.4 Neurulation

The first indication of the neural plate in human embryos is a median sulcus around 23 days of development. At approximately 25 days (stage 9), this **neural groove** is deeper and longer. Its rostral half represents the forebrain, its caudal half mainly the hindbrain (Fig. 1.6). The **neural folds** of the forebrain are conspicuous. The **mesencephalic flexure** appears, and allows a first subdivision of the brain into three major divisions in the still unfused neural folds (O'Rahilly 1973; O'Rahilly and Gardner 1979; Müller and O'Rahilly 1983, 1997; Jirásek 2001, 2004): the forebrain or **prosencephalon**, the midbrain or **mesencephalon**, and the hindbrain or **rhombencephalon** (Figs. 1.7, 1.8). The otic discs, the first indication of the internal ears, can also be recognized. At stage 10, the two subdivisions of the forebrain, the telen-

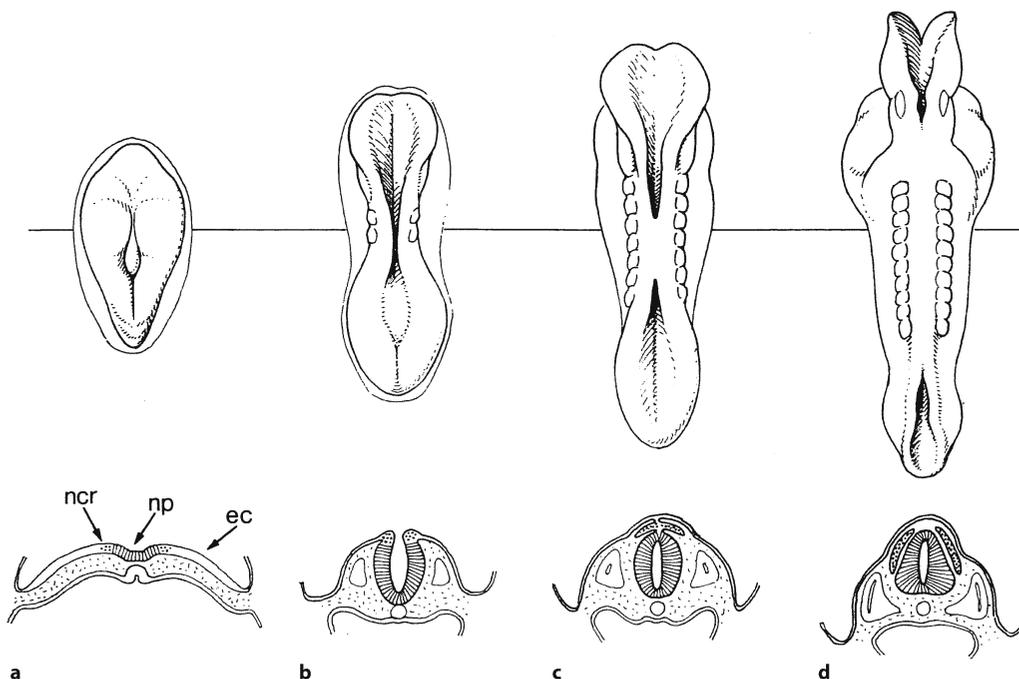


Fig. 1.6 The formation of the neural tube and neural crest. Dorsal views and transverse sections are shown for human embryos of stages 8 (**a**), 9 (**b**), 10 (**c**, seven somites) and 10 (**d**, ten somites). *ec* ectoderm, *ncr* neural crest, *np* neural plate

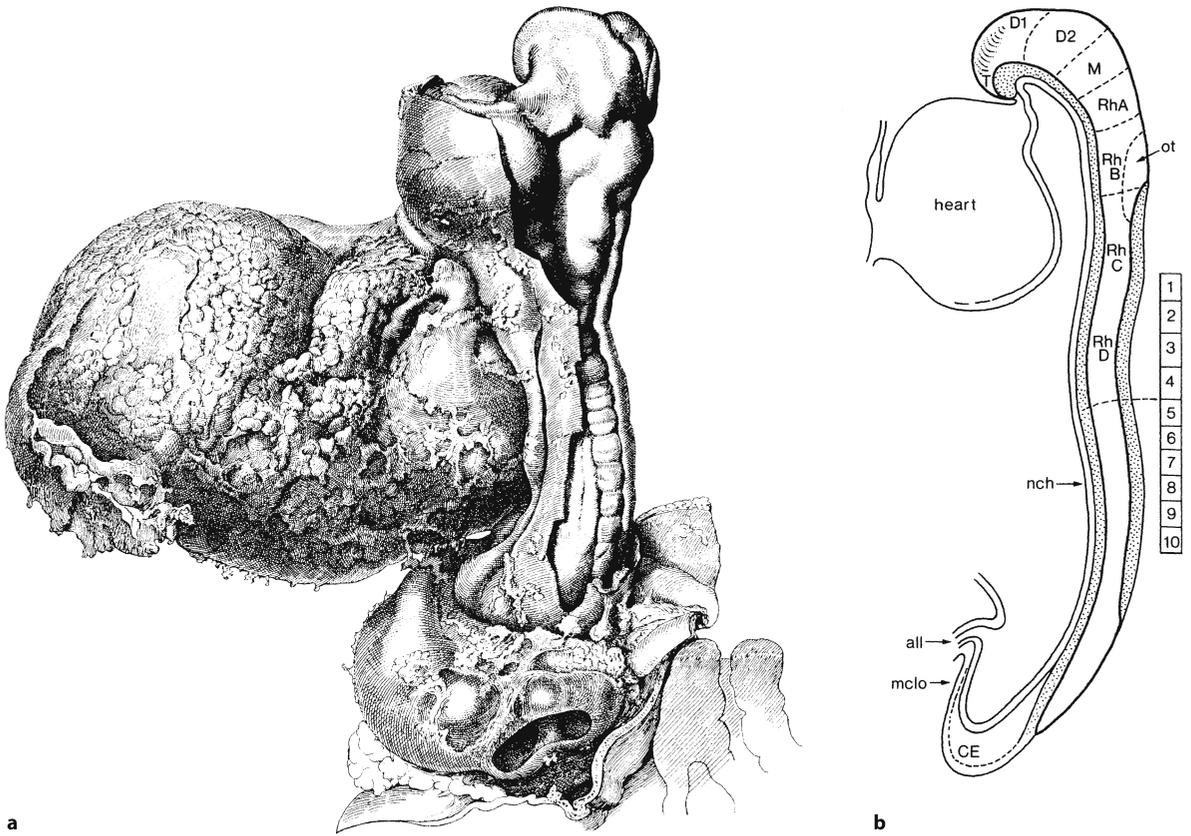


Fig. 1.7 Corner's ten-somite embryo (**a**). **b** A median section, showing the subdivision of the brain into the primary neuromeres. *all* allantois, *CE* caudal eminence, *D1*, *D2* diencephalic neuromeres, *M* mesomere, *mclo* membrana cloacalis, *nch* notochord, *ot* otocyst, *RhA–RhD* primary rhombomeres, *T* telencephalic neuromere 1–10 first ten somites. (**a** Illustrated by James Didusch, from Corner 1929, with permission; **b** after O'Rahilly and Müller 1987)

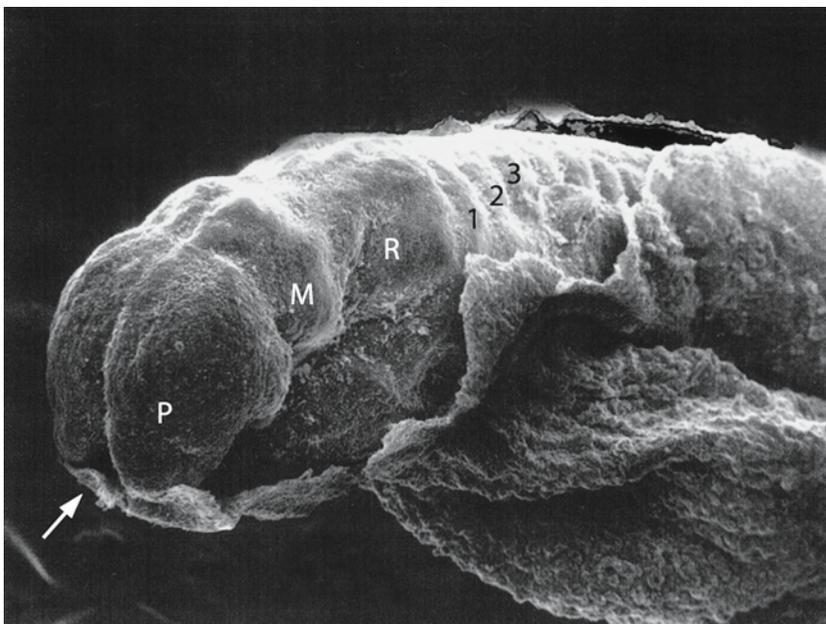


Fig. 1.8 Scanning electron micrograph of a 26–27-day-old, 2.5-mm embryo with 14 paired somites (stage 11). The *arrow* indicates the rostral neuropore. *P* prosencephalon, *M* mesencephalon, *R* rhombencephalon, 1–3 first three somites. (From Jirásek 2004, with permission)

cephalon and the **diencephalon**, become evident (Müller and O’Rahilly 1985). An **optic sulcus** is the first indication of the developing eye. Closure of the neural groove begins near the junction between the future brain and the spinal cord. Rostrally and caudally, the cavity of the developing neural tube communicates via the **rostral** and **caudal neuropores** with the amniotic cavity. The rostral neuropore closes at about 30 days (stage 11), and the caudal neuropore about 1 day later (stage 12). The site of final closure of the rostral neuropore is at the site of the embryonic lamina terminalis (O’Rahilly and Müller 1999). The closure of the neural tube in human embryos is generally described as a continuous process that begins at the level of the future cervical region, and proceeds both rostrally and caudally (O’Rahilly and Müller 1999, 2001). Nakatsu et al. (2000), however, provided evidence that neural tube closure in humans may be initiated at multiple sites as in mice and other animals. **Neural tube defects** are among the most common of human malformations (Chap. 4).

When the surface ectodermal cells of both sides fuse, the similarly fusing neuroectodermal cells of the neural folds give off neural crest cells (Fig. 1.6). These cells arise at the neurosomatic junction. The **neural crest** cells migrate extensively to generate a large diversity of differentiated cell types (Le Douarin and Kalcheim 1999; Chap. 5), including (1) the spinal, cranial and autonomic ganglia, (2) the medulla of the adrenal gland, (3) the melanocytes, the pigment-containing cells of the epidermis, and (4) many of the skeletal and connective tissues of the head. The final phase of primary neurulation is the separation of neural and surface ectoderm by mesenchyme. Failure to do so may lead to an encephalocele, at least in rats (O’Rahilly and Müller 2001). Malformations of the neural crest (**neurocristopathies**) may be accompanied by developmental disorders of the CNS (Chap. 5).

Detailed **fate map** studies are available for amphibians and birds (Chap. 2). The organization of vertebrate neural plates appears to be highly conserved. This conservation probably extends to mammals, for which detailed fate maps are more difficult to obtain. Nevertheless, available data (Rubinstein and Beachy 1998; Rubinstein et al. 1998; Inoue et al. 2000) show that in mice ventral parts of the forebrain such as the hypothalamus and the eye vesicles arise from the medial part of the rostral or prosencephalic part of the neural plate (Fig. 1.10c). Pallial as well as subpallial parts of the telencephalon arise from the lateral parts of the prosencephalic neural plate. The lateral border of this part of the neural plate forms the dorsal, median part of the telencephalon and the commissural plate from which the anterior commissure and the corpus callosum arise.

Initially, the wall of the neural tube consists of a single layer of neuroepithelial cells, the **germinal neuroepithelium** or **matrix layer**. As this layer thickens, it gradually acquires the configuration of a pseudostratified epithelium. Its nuclei become arranged in more and more layers, but all elements remain in contact with the external and internal surface. Mitosis occurs on the internal, ventricular side of the cell layer only (Figs. 2.18, 2.19), and migrating cells form a second layer around the original neural tube. This layer, the **mantle layer** or **intermediate zone**, becomes progressively thicker as more cells are added to it from the germinal neuroepithelium that is now called the **ventricular zone**. The cells of the intermediate zone differentiate into neurons and glial cells. Radial glial cells are present during early stages of neurogenesis. Most radial glial cells transform into astrocytes (Chap. 2). The neurons send axons into an outer layer, the **marginal zone**. The mantle layer, containing the cell bodies, becomes the **grey matter**, and the axonal, marginal layer forms the **white matter**. In the spinal cord, this three-zone pattern is retained throughout development.

Secondary proliferative compartments are found elsewhere in the brain. The **external germinal** or **granular layer** is confined to the cerebellum. It develops from the ventricular zone of the rhombic lip, a thickened germinal zone in the rhombencephalic alar plate, and gives rise to the granule cells of the cerebellum. The **subventricular zone** is found in the lateral and basal walls of the telencephalon. This zone gives rise to a large population of glial cells and to the granule cells of the olfactory bulb.

1.5 Development of the Spinal Cord

After neurulation, the **spinal cord** can be divided into dorsal **alar plates** derived from lateral parts of the neural plate, and ventral **basal plates** derived from its medial parts (Fig. 1.9). The alar and basal plates are separated by the **sulcus limitans** of His (1880). The alar plates are united by a small roof plate, and the basal plates by a thin floor plate. The alar plates and incoming dorsal roots form the afferent or sensory part of the spinal cord, whereas the basal plate and its exiting ventral root form the efferent or motor part. The spinal ganglia arise from the neural crest. The development of the alar and basal plates is induced by **extracellular signalling molecules**, secreted by the notochord and the adjacent ectoderm (Fig. 1.9). The protein SHH of the *SHH* gene in the notochord induces the formation of the floor plate. In its turn, the floor plate induces the formation of motoneurons in the basal plate. Bone morphogenetic proteins (BMPs) from the ectoderm induce the formation of the alar and roof plates and of the neural crest. BMP4 and

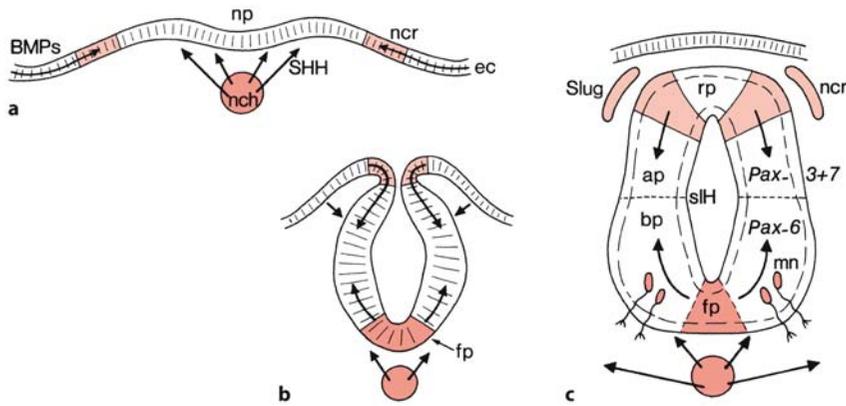


Fig. 1.9 The development of the spinal cord and the dorsalizing (bone morphogenetic proteins, *BMPs*) and ventralizing (Sonic hedgehog, *SHH*) factors involved. **a** *SHH* in the notochord (*nch*, red) induces the formation of the floor plate (*fp*), after which *SHH* in the floor plate induces the formation of motoneurons (**b, c**). *BMP4* and *BMP7* (light red) from the ectoderm

(**ec**) induce *Slug* in the neural crest (*ncr*) and support the expression of *Pax3* and *Pax7* in the dorsal part of the spinal cord. *SHH* suppresses the expression of these transcription factors. *ap* alar plate, *bp* basal plate, *mn* motoneurons, *np* neural plate, *rp* roof plate, *slH* sulcus limitans of His. (After Carlson 1999)

BMP7 induce the expression of the transcription factor ‘*Slug*’ in the neural crest and the expression of certain *Pax* transcription factors in the alar plates. *SHH* suppresses these dorsal *Pax* genes in the ventral half of the spinal cord. Many other genes are involved in the specification of the various types of neurons in the spinal cord (Chap. 6). Motoneurons are the first neurons to develop (Windle and Fitzgerald 1937; Bayer and Altman 2002). They appear in the uppermost spinal segments at approximately embryonic day 27 (about Carnegie stage 13/14). At this time of development also dorsal root ganglion cells are present. Dorsal root fibres enter the spinal grey matter very early in development (Windle and Fitzgerald 1937; Konstantinidou et al. 1995; Chap. 6). The first synapses between primary afferent fibres and spinal motoneurons were found in a stage 17 embryo (Okado et al. 1979; Okado 1981). Ascending fibres in the dorsal funiculus have reached the brain stem at stage 16, i.e. at about 37 postovulatory days (Müller and O’Rahilly 1989). The first descending supraspinal fibres from the brain stem have extended into the spinal cord at stage 14 (Müller and O’Rahilly 1988b). Even the late developing pyramidal tract extends as far caudally as the spinomedullary junction at the end of the embryonic period (Müller and O’Rahilly 1990c; ten Donkelaar 2000). The spinal cord then still reaches the end of the vertebral canal. During the fetal period, it ‘ascends’ to sacral and later lumbar levels (Chap. 6).

1.6 Pattern Formation of the Brain

Prospective subdivisions of the brain are specified through **pattern formation** which takes place in two directions: from medial to lateral, and from rostral to caudal (Lumsden and Krumlauf 1996; Rubinstein and Beachy 1998; Fig. 1.10). Mediolateral or ventrodorsal pattern formation generates longitudinal areas such as the alar and basal plates, and rostrocaudal pattern formation generates transverse zones (one or more neuromeres). Most likely, the rostrocaudal regionalization of the neural plate is induced already during gastrulation (Nieuwkoop and Albers 1990). In amphibians, the first mesoderm to ingress gives rise to the anterior head mesoderm. The mesoderm that follows will form the chordamesoderm and more lateral mesodermal structures. The anterior mesoderm differs from the chordamesoderm also in the genes that it expresses. Signals from both the anterior mesoderm and the chordamesoderm initiate neural development by inducing neural tissue of an anterior type, i.e. forebrain and midbrain, in the overlying ectoderm along its entire anteroposterior length. A second signal from chordamesoderm alone converts the overlying neuroectoderm induced by the first signal into a posterior type of neural tissue, i.e. hindbrain and spinal cord (Chap. 2). Endodermal signalling molecules also play an important role in the induction of the rostral part of the CNS (de Souza and Niehrs 2000).

Developmental gene expression studies show that the vertebrate CNS can be divided into three regions. The anterior region comprises the forebrain and most of the midbrain, and is characterized by expres-

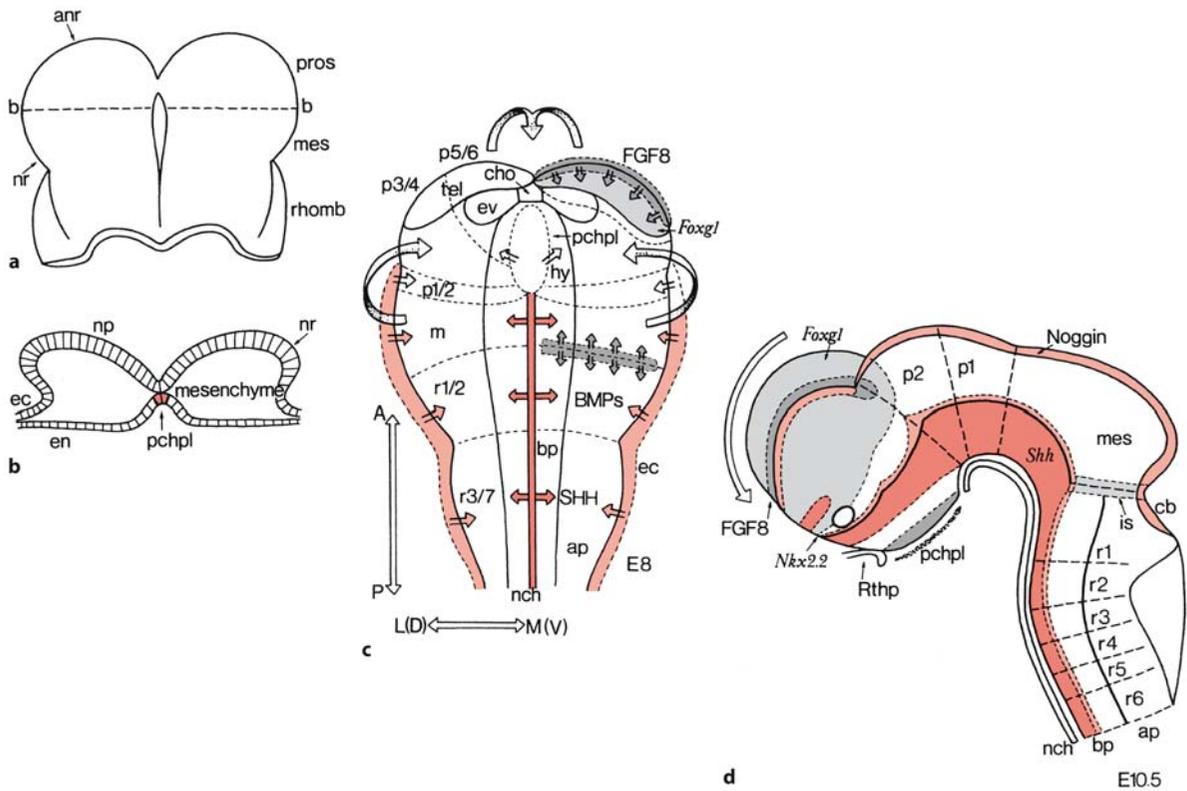


Fig. 1.10 Bauplan and pattern formation of the mouse brain. **a** The dorsal view of the rostral part of the neural plate (*np*) shows the approximate locations of the prosencephalon (*pros*), mesencephalon (*mes*) and rhombencephalon (*rhomb*), and **b** the transverse section shows the structures involved. The expression of some genes involved in the patterning of the brain is shown in a dorsal view of the neural plate of an E8 mouse (**c**) and in a median section through the neural tube at E10.5 (**d**). The arrows indicate the morphogenetic processes involved in the closure of the neural tube. The expression of lateralizing (*L*) or dorsalizing (*D*) signalling mole-

cules such as BMPs is indicated in *light red*, the medializing (*M*) or ventralizing (*V*) factor SHH in *red*, the fibroblast growth factor 8 (*FGF8*) in *dark grey* and brain factor 1 (*Foxg1*) in *grey*. Medial signals induce the basal plate (*bp*), whereas lateral signals induce the alar plate (*ap*). *anr* anterior neural ridge, *cb* cerebellum, *cho* chiasma opticum, *ec* ectoderm, *en* endoderm, *ev* eye vesicle, *hy* hypothalamus, *is* isthmus, *m* mesencephalon, *nch* notochord, *nr* neural ridge, *pchpl* prechordal plate, *p1*, *p6* prosomeres, *Rthp* Rathke's pouch, *r1*–*r7* rhombomeres, *tel* telencephalon. (After Rubinstein and Beachy 1998; Rubinstein et al. 1998)

sion of the **homeobox genes** *Emx* and *Otx*. The middle division comprises the posterior part of the midbrain and most of the first rhombomere. It is known as the midbrain–hindbrain boundary (MHB) or isthmocerebellar region. The third region comprises the rhombencephalon and spinal cord, and is characterized by *Hox* gene expression.

Longitudinal patterning centres are present along the ventral (notochord and prechordal plate, and later the floor plate) and dorsal (epidermal–neuroectodermal junction, and later the roof plate) aspects of the neural plate and early neural tube. Medial, i.e. **ventralizing**, signals such as SHH play an important role during the formation of the primordia of the basal plate. SHH induces the formation of motoneurons in the spinal cord and brain stem (Chap. 6). Lat-

eral, i.e. **dorsalizing**, signals such as BMPs from the adjacent ectoderm induce the formation of the alar plate and the dorsal part of the forebrain. SHH is not only responsible for dorsoventral patterning in the CNS, but also plays a role during the specification of oligodendrocytes, the proliferation of neural precursors and the control of axon growth (Marti and Bovolenta 2002). The BMPs also have a variety of functions (Mehler et al. 1997). **Holoprosencephaly**, a defect in brain patterning, is the most common structural anomaly of the developing forebrain (Golden 1998; Muenke and Beachy 2000; Sarnat and Flores-Sarnat 2001; Chap. 9).

Specialized, **transverse patterning centres** are present at specific anteroposterior locations of the neural plate such as the anterior neural ridge and the

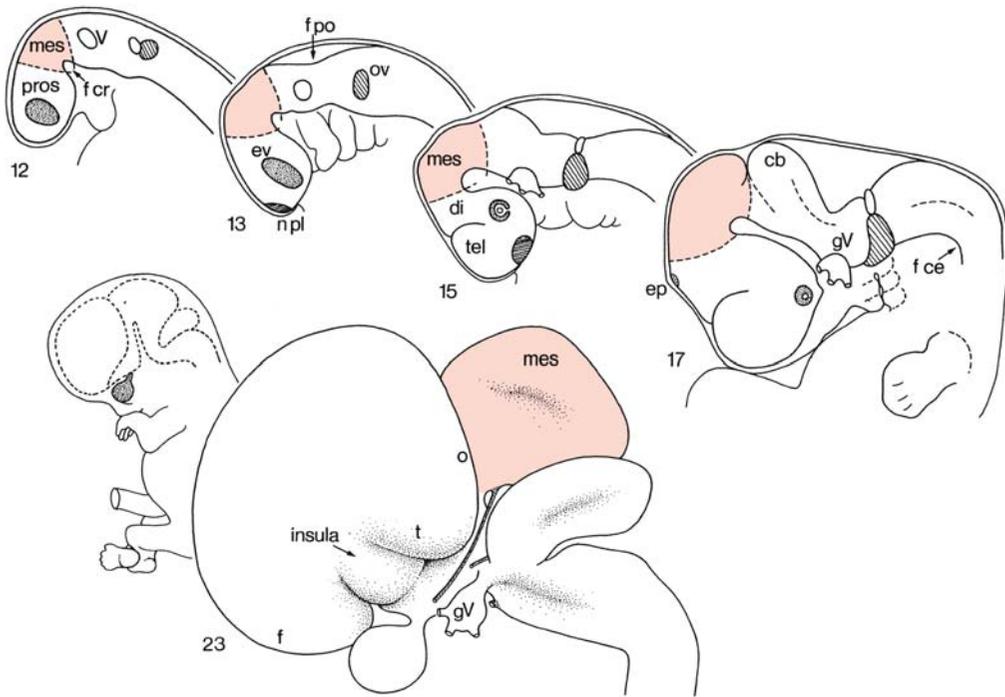


Fig. 1.11 Lateral views of the developing brain in Carnegie stages 12, 13, 15, 17 and 23. The mesencephalon is indicated in light red. *cb* cerebellum, *di* diencephalon, *ep* epiphysis, *ev* eye vesicle, *f* frontal lobe, *f ce* flexura cervicalis, *f cr* flexura cranialis,

f po flexura pontina, *gv*, *V* trigeminal ganglion, *mes* mesencephalon, *n pl* nasal placode, *o* occipital lobe, *pros* prosencephalon, *t* temporal lobe, *tel* telencephalon. (After O’Rahilly and Müller 1999)

already mentioned MHB (Fig. 1.10). They provide a source of secreted factors that establish the regional identity in adjacent domains of the neural tube. The posterior limit of *Otx2* expression marks the anterior limit of the MHB, whereas the anterior limit of *Gbx2* expression marks its posterior limit. In *Otx2* knockout mice, the rostral neuroectoderm is not formed, leading to the absence of the prosencephalon and the rostral part of the brain stem (Acampora et al. 2001; Wurst and Bally-Cuif 2001). In *Gbx2* knockouts, all structures arising from the first three rhombomeres, such as the cerebellum, are absent. Cells in the MHB (the **isthmus organizer**) secrete fibroblast growth factor (FGFs) and *Wnt* proteins which are required for the differentiation and patterning of the midbrain and hindbrain (Rhinn and Brand 2001). Signals from the **anterior neural ridge** including FGF8 regulate the expression of *Foxg1* (earlier known as *brain factor 1*, *BF1*), a transcription factor that is required for normal telencephalic and cortical morphogenesis (Rubinstein and Beachy 1998; Monuki and Walsh 2001). Although much of our insight into these patterning mechanisms relies on studies in mice, humans are subject to a wide variety of naturally occurring mutations (Chap. 9).

1.7 Early Development of the Brain

Lateral and medial views of the developing brain are shown in Figs. 1.11 and 1.12. The neural tube becomes bent by three flexures: (1) the **mesencephalic flexure** at the midbrain level, already evident before fusion of the neural folds; (2) the **cervical flexure**, situated at the junction between the rhombencephalon and the spinal cord, and (3) the **pontine flexure** in the hindbrain. The three main divisions of the brain (prosencephalon, mesencephalon and rhombencephalon) can already be recognized when the neural tube is not yet closed. The forebrain soon divides into an end portion, the **telencephalon**, and the **diencephalon** that can be identified because it gives rise to the optic vesicles (Fig. 1.12). With the development of the **cerebellum**, the pons and the trigeminal nerve, the division of the hindbrain into a rostral part, the **metencephalon**, and a caudal part, the **medulla oblongata** or **myelencephalon**, becomes evident. The junction between the hindbrain and midbrain is relatively narrow and is known as the **isthmus rhombencephali**. The first part of the telencephalon that can be recognized is the **telencephalon medium** or **impar**. By stage 15, the future cerebral hemispheres can be recognized. The **cerebral hemispheres**

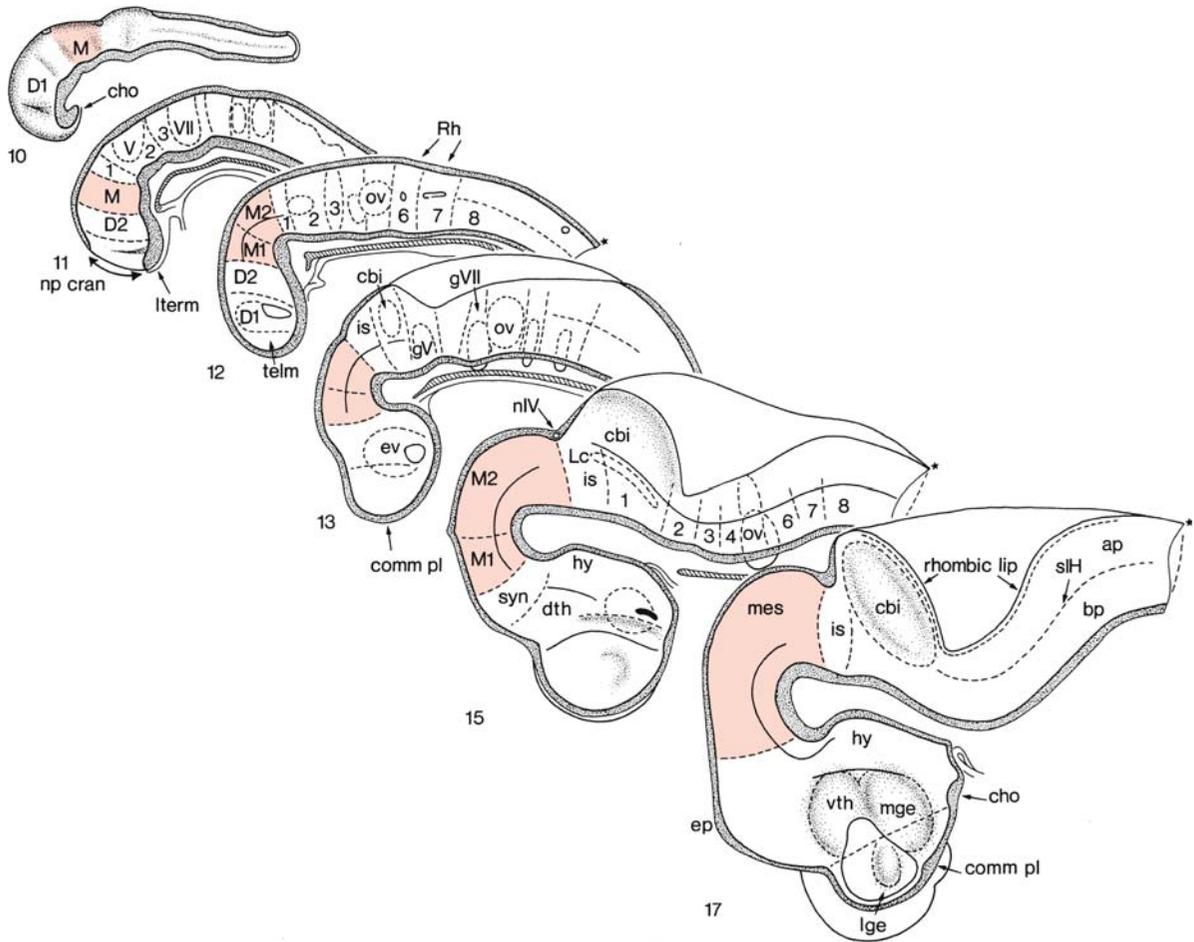


Fig. 1.12 Medial views of the developing brain in Carnegie stages 10–13, 15 and 17. The mesomeres (*M*, *M1*, *M2*) and the mesencephalon (*mes*) are indicated in light red. Asterisks indicate the spinomedullary junction. *ap* alar plate, *bp* basal plate, *cbi* internal cerebellar bulge, *cho* chiasma opticum, *comm pl* commissural plate, *D1*, *D2* diencephalic neuromeres, *dth* dorsal thalamus, *ep* epiphysis, *ev* eye vesicle, *gV* trigeminal

ganglion, *gVII* facial ganglion, *hy* hypothalamus, *is* isthmus, *Lc* locus coeruleus, *lge* lateral ganglionic eminence, *lterm* lamina terminalis, *mge* medial ganglionic eminence, *np cran* cranial neuropore, *nIV* nervus trochlearis, *ov* otic vesicle, 1–8 rhombomeres, *slH* sulcus limitans of His, *syn* synencephalon, *telm* telencephalon medium, *vth* ventral thalamus. (After O’Rahilly and Müller 1999)

enlarge rapidly so that by the end of the embryonic period they completely cover the diencephalon. Frontal, temporal and occipital poles and the insula become recognizable (Fig. 1.11), whereas an olfactory bulb becomes visible on the ventral surface.

1.7.1 Imaging of the Embryonic Brain

The introduction of the ultrasound method has opened new possibilities for studying the human embryonic brain. The use of the transvaginal route has so greatly improved the image quality that a detailed description of the living embryo and early fetus has become possible (Fig. 1.13). Ultrasound data show

agreement with the developmental time schedule described in the Carnegie staging system (Blaas et al. 1994, 1995a, b; Blaas and Eik-Nes 1996; van Zalen-Sprock et al. 1996; Blaas 1999; Pooh et al. 2003). Human development and possible maldevelopment can be followed in time. The extension of the ultrasound techniques to three dimensions has made it possible to reconstruct the shape of the brain ventricles and to measure their volumes (Blaas et al. 1995a, b; Blaas 1999; Blaas and Eik-Nes 2002). Anomalies of the ventricular system such as diverticula are rare (Hori et al. 1983, 1984a). Accessory ventricles of the posterior horn are relatively common and develop postnatally (Hori et al. 1984b; Tsuboi et al. 1984).

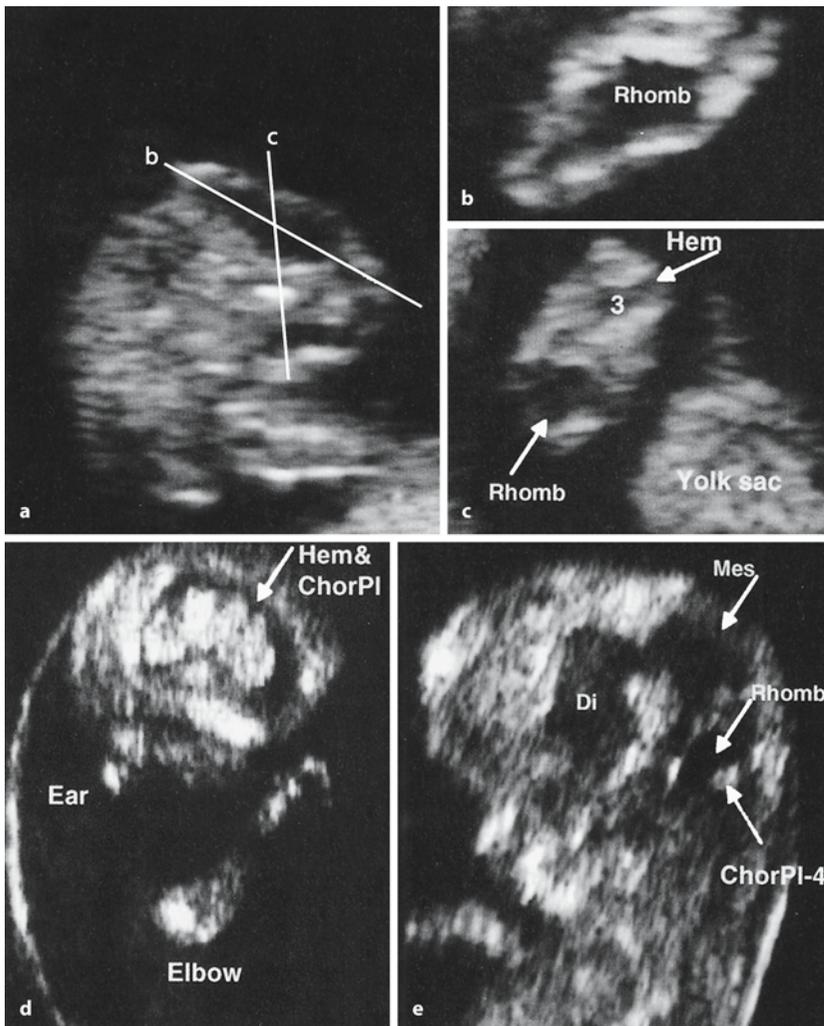


Fig. 1.13 Ultrasound images in human embryos of 7.5 (a–c), 9.5 (d) and 10 (e) weeks of gestation with crown–rump lengths of 11, 29 and 33 mm, respectively. *ChorPI-4* choroid plexuses of lateral and fourth ventricles, *Di* diencephalon, *Hem* cerebral hemisphere, *Mes* mesencephalon, *Rhomb* rhombencephalon, *3* third ventricle. (Kindly provided by Harm-Gerd K. Blaas, Trondheim)

1.7.2 Neuromeres

Morphological segments or neuromeres of the brain were already known to von Baer (1828), and were described for the human brain by Bartelmez (1923) and Bergquist (1952), and for many other vertebrates (Nieuwenhuys 1998). **Neuromeres** are segmentally arranged transverse bulges along the neural tube, particularly evident in the hindbrain (Fig. 1.14). Only recently, interest in neuromeres was greatly renewed owing to the advent of gene-expression studies on development, starting with the homeobox genes. The expression of *HOX* genes in the developing human brain stem is directly comparable to that of *Hox* genes in mice (Vieille-Grosjean et al. 1997). Each rhombomere is characterized by a unique combination of *Hox* genes, its *Hox* code. The timing and sequence of appearance of neuromeres and their derivatives were studied in staged human embryos (Müller and O’Rahilly 1997; Fig. 1.15). The neuromeres of the forebrain, midbrain and hindbrain

were determined morphologically on the basis of sulci, mitotic activity in the walls and fibre tracts. Six **primary neuromeres** appear already at stage 9 when the neural folds are not fused (Fig. 1.7b): prosencephalon, mesencephalon and four rhombomeres (A–D). Sixteen **secondary neuromeres** can be recognized from about stage 11. They gradually fade after stage 15 (Fig. 1.12). Eight **rhombomeres** (Rh1–Rh8), an **isthmic neuromere** (I), two **mesomeres** (M1, M2) of the midbrain, two **diencephalic neuromeres** (D1, D2) and one **telencephalic neuromere** (T) can be distinguished. The diencephalic neuromere D2 can be further subdivided into the **synencephalon**, the **parencephalon caudalis** and the **parencephalon rostralis**. Neuromere D1 gives rise to the eye vesicles and the medial ganglionic eminences (Müller and O’Rahilly 1997).

Each neuromere has **alar** (dorsal) and **basal** (ventral) components. In the developing spinal cord and brain stem, the **sulcus limitans** divides the proliferative compartments into alar and basal plates. The



Fig. 1.14 Dorsal view of a malformed embryo (Carnegie stage 14) showing the bulging of several rhombomeres (kindly provided by Kohei Shiota, Kyoto)

mesencephalic part of the sulcus is not continuous with a more rostral, diencephalic sulcus (Keyser 1972; Gribnau and Geijsberts 1985; Müller and O’Rahilly 1997; Fig. 1.12). Studies in mice (Bulfone et al. 1993; Puelles and Rubinstein 1993; Shimamura et al. 1995; Rubinstein et al. 1998) show that some genes are expressed in the alar plate only, others only in the basal plate (Fig. 1.10). One gene, *Nkx2.2*, is expressed along the longitudinal axis of the brain, ending in the chiasmatic region. On the basis of these findings, in all murine prosomeres alar and basal parts are distinguished (Rubinstein et al. 1998; Puelles et al. 2000; Puelles and Rubinstein 2003).

In mice (Fig. 2.9b), the prosencephalon has been divided into six **prosomeres**, numbered P1–P6 from caudal to rostral. Prosomeres P1–P3 form the diencephalon: P1 is the synencephalon, P2 the parencephalon caudalis and P3 the parencephalon rostralis. The alar component of the synencephalon forms the preectum, that of the caudal parencephalon the dorsal thalamus and epithalamus and that of the rostral parencephalon the ventral thalamus. The basal components jointly form the pre-rubral tegmentum. Prosomeres P4–P6, together known as a protosegment, form the **secondary prosencephalon** (Rubinstein et al. 1998; Puelles et al. 2000; Puelles and Rubinstein 2003), from which the hypothalamus, both optic vesicles and the telencephalon arise. The basal parts of the secondary prosencephalon give rise to the various subdivisions of the hypothalamus, whereas from the alar parts prethalamalic areas and the entire telencephalon, i.e. the cerebral cortex and the subcortical centers such as the basal ganglia, arise. The main differences between human and murine neuromeres concern the prosomeres. Puelles and Verney (1998) applied the prosomeric subdivision to the human forebrain.

Fig. 1.15 Median section of a stage 13 embryo. Rhombomeres 2, 4 and 6 can be recognized by ventral bulges. *cb* cerebellum, *is* isthmus, *M1*, *M2* mesomeres, *Rp* Rathke’s pouch, *syn* synencephalon, *tel* telencephalon, *v4* fourth ventricle. (From O’Rahilly 1975, with permission)



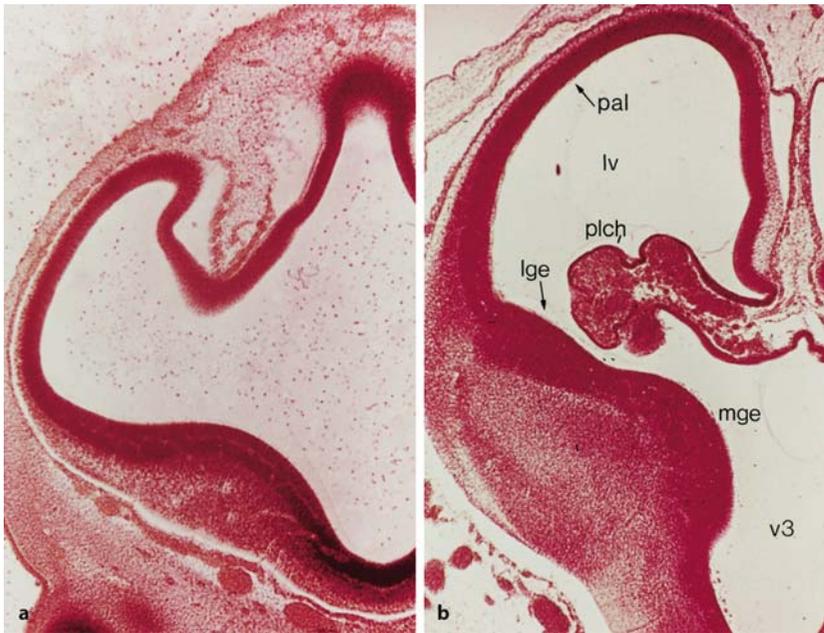


Fig. 1.16 Transverse sections through the human forebrain, showing the developing ganglionic or ventricular eminences at stages 17 (**a**) and 20 (**b**), respectively. *lge* lateral ganglionic eminence, *lv* lateral ventricle, *mge* medial ganglionic eminence, *pal* pallium, *plch* plexus choroideus, *v3* third ventricle. (From O’Rahilly 1975, with permission)

1.7.3 The Ganglionic Eminences

At first, each cerebral hemisphere consists of a thick basal part, the **subpallium**, giving rise to the basal ganglia, and a thin part, the **pallium**, that becomes the future cerebral cortex. The subpallium appears as medial and lateral elevations, known as the **ganglionic** (*Ganglionhügel* of His 1889) or **ventricular eminences** (Fig. 1.16). The caudal part of the ventricular eminences is also known as the **caudal ganglionic eminence**, and primarily gives rise to parts of the amygdala. The **medial ganglionic eminence** is derived from the diencephalon, and is involved in the formation of the globus pallidus. The larger **lateral ganglionic eminence** is derived from the telencephalon, and gives rise to the caudate nucleus and the putamen. As the internal capsule develops, its fibres separate the caudate nucleus from the putamen, and the thalamus and the subthalamus from the globus pallidus. Both the lateral and the medial ventricular eminences are also involved in the formation of the cerebral cortex. The pyramidal cells of the cerebral cortex arise from the ventricular zone of the pallium, but the cortical GABAergic interneurons arise from both ganglionic eminences, the medial eminence in particular (Parnavelas 2000; Anderson et al. 2001; Marín and Rubinstein 2001; Chap. 9). The caudal part of the ganglionic eminence also gives rise to a contingent of GABAergic neurons for dorsal thalamic association nuclei such as the pulvinar through a transient fetal structure, the **gangliothalamic body** (Rakić and Sidman 1969; Letinić and Kostović 1997; Letinić and Rakic 2001).

1.8 Fetal Development of the Brain

The most obvious changes in the fetal period are (1) the outgrowth of the cerebellar hemispheres and the formation of its median part, the vermis, (2) the continuous expansion of the cerebral hemispheres, the formation of the temporal lobe and the formation of sulci and gyri and (3) the formation of commissural connections, the corpus callosum in particular.

1.8.1 The Cerebellum

The development of the **cerebellum** takes place largely in the fetal period (Fig. 1.17). The cerebellum arises bilaterally from the alar layers of the first rhombomere (Fig. 1.12). Early in the fetal period, the two cerebellar primordia are said to unite dorsally to form the vermis. Sidman and Rakic (1982), however, advocated Hochstetter’s (1929) view that such a fusion does not take place, and suggested one cerebellar primordium (the **tuberculum cerebelli**). The tuberculum cerebelli consists of a band of tissue in the dorsolateral part of the alar plate that straddles the midline in the shape of an inverted V. The arms of the V are directed caudally as well as laterally, and thicken enormously, accounting for most of the early growth of the cerebellum. The rostral, midline part of the V, however, remains small and relatively inconspicuous. The further morphogenesis of the cerebellum can be summarized as follows: (1) the caudally and laterally directed limbs of the tuberculum cerebelli thicken rapidly during the sixth postovulatory week and bulge downwards into the fourth ventricle

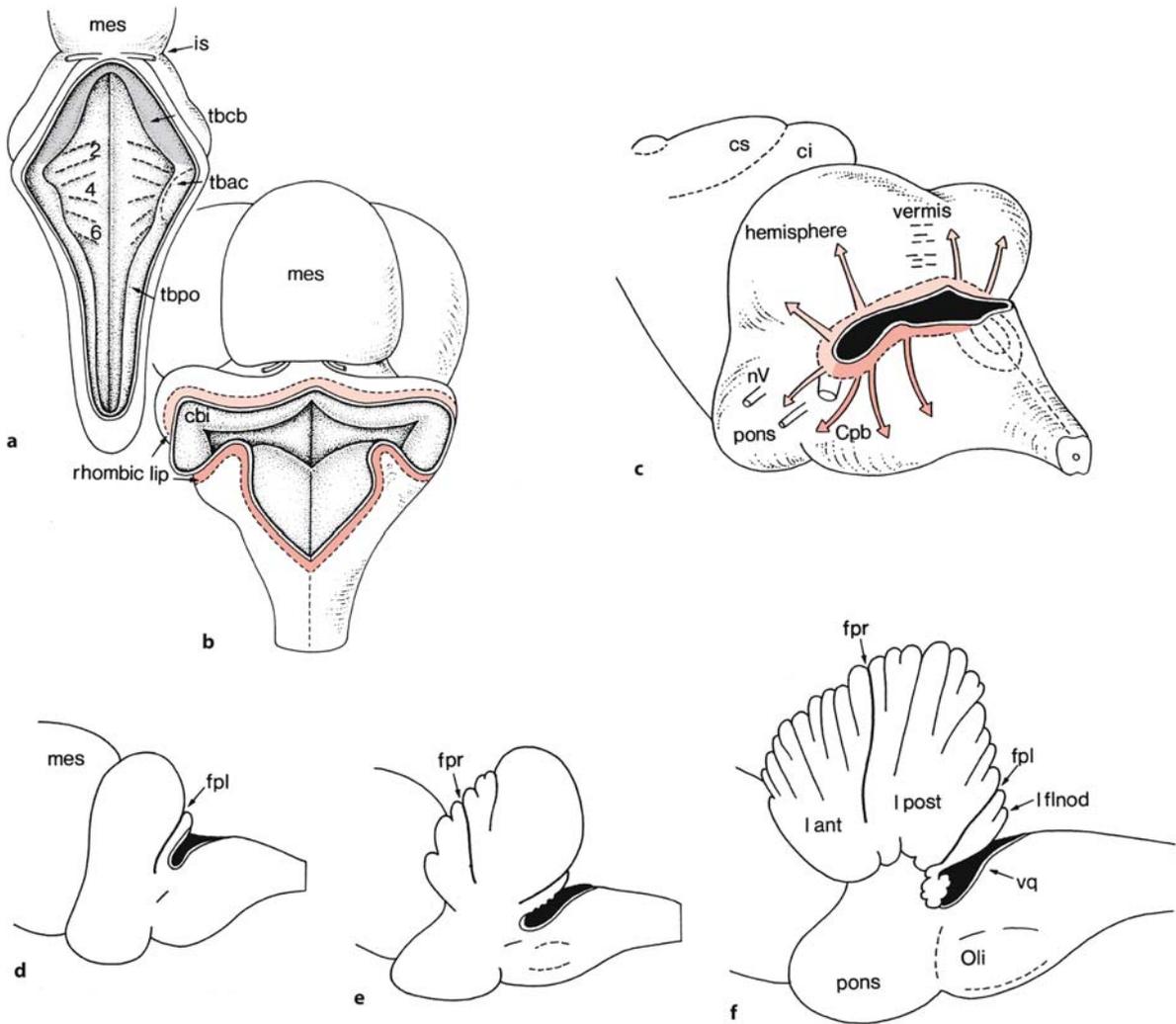


Fig. 1.17 Embryonic (a, b) and fetal (c–f) development of the human cerebellum: **a** at approximately 4 weeks; **b** at the end of the embryonic period; **c–f** at 13 weeks (c, d), and 4 (e) and 5 (f) months of development. The V-shaped tuberculum cerebelli (tbc) is indicated in grey, and the upper and lower rhombic lips in light red and red, respectively. *cbi* internal cerebellar bulge, *ci* colliculus inferior, *Cpb* corpus pontobulbare, *cs* col-

liculus superior, *fpl* fissura posterolateralis, *fpr* fissura prima, *is* isthmus, *lant* lobus anterior, *lfnod* lobus flocculonodularis, *lpost* lobus posterior, *mes* mesencephalon, *nV* trigeminal nerve, *Oli* olivarius inferior, *tbac* tuberculum acusticum, *tbpo* tuberculum ponto-olivare, *vq* vermiculus quartus, 2, 4, 6 rhombomeres. (a After Streeter 1911, 1912; Jakob 1928; b after Hochstetter 1929; c–f after Streeter 1911, 1912)

(on each side the internal cerebellar bulge or *innerer Kleinhirnwulst* of Hochstetter which together form the **corpus cerebelli**); (2) during the seventh week, the rapidly growing cerebellum bulges outwards as the external cerebellar bulges (*äusserer Kleinhirnwulst* of Hochstetter) which represent the **flocculi**, which are delineated by the posterolateral fissures; (3) during the third month of development, i.e. early in the fetal period, growth of the midline component accelerates and begins to fill the gap between the limbs of the V, thereby forming the **vermis**; and (4) by the 12th to 13th weeks of development, outward, lat-

eral and rostral growth processes have reshaped the cerebellum to a transversely oriented bar of tissue overriding the fourth ventricle. At the 12th week, fissures begin to form transverse to the longitudinal axis of the brain, first on the vermis and then spreading laterally into the hemispheres. By stage 18 (approximately 44 days), the internal cerebellar swellings contain the dentate nuclei, the first sign of the superior cerebellar peduncles can be seen around stage 19 (about 48 days) and the cerebellar commissures appear at the end of the embryonic period (Müller and O’Rahilly 1990b).

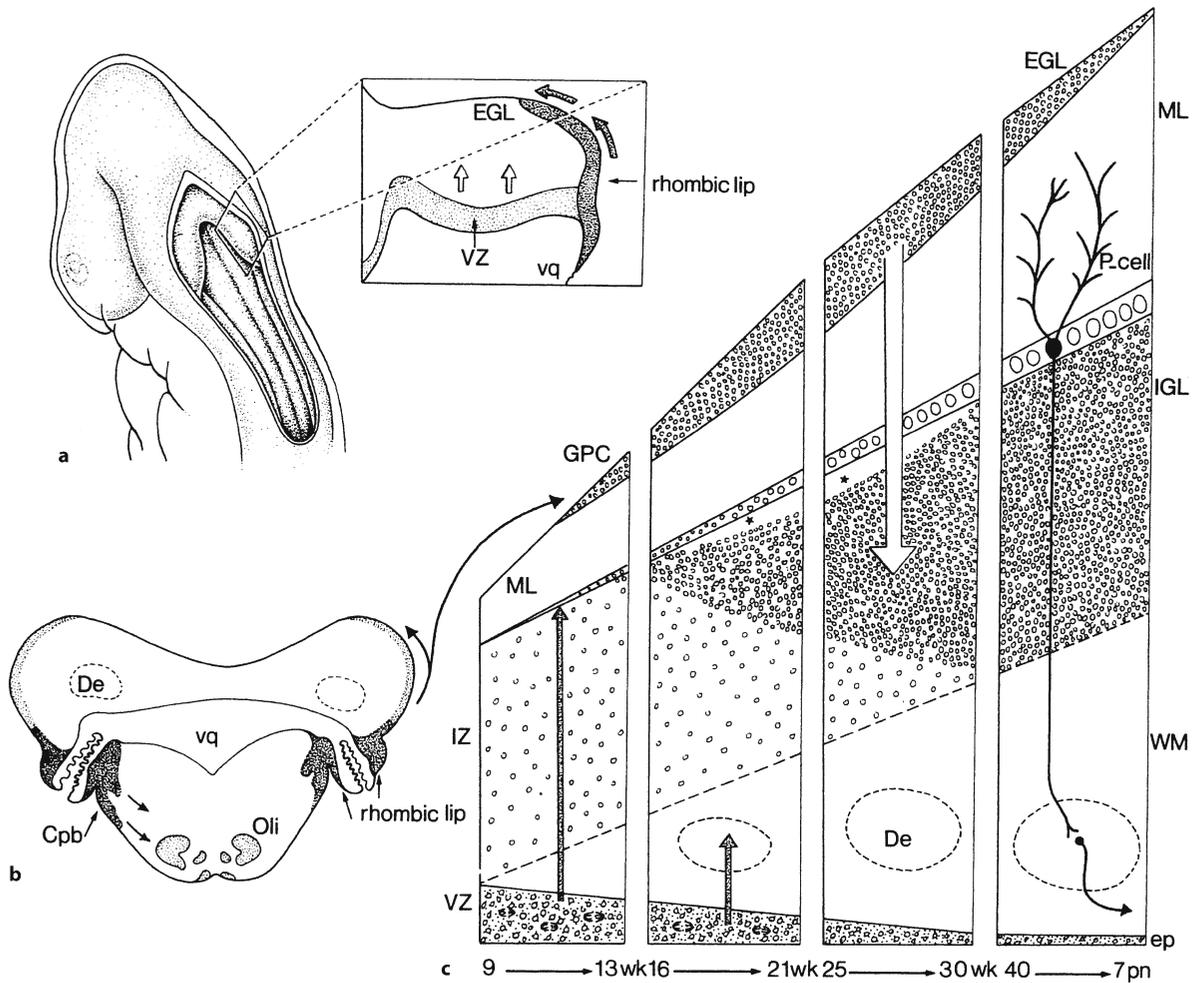


Fig. 1.18 Overview of the histogenesis of the cerebellum. **a** A dorsolateral view of a human embryo and part of the tuberculum cerebelli enlarged, showing the two proliferative compartments: the ventricular zone (VZ), giving rise to Purkinje cells and the deep cerebellar nuclei, and the external germinal or granular layer (EGL), giving rise to the granule cells. **b** The position of the rhombic lip in a transverse section at the level of the lateral recess of the fourth ventricle. The upper rhombic lip is found lateral to the lateral recess, and the lower rhombic lip medial to the recess. **c** The formation of the layers of

the cerebellum in four periods from the early fetal period until 7 weeks postnatally. The lamina dissecans is indicated with *asterisks*. The *arrows* in **a-c** show the migration paths. *Cpb* corpus pontobulbare, *De* dentate nucleus, *ep* ependyma, *GPC* granule precursor cells, *IGL* internal granular layer, *IZ* intermediate zone, *ML* molecular layer, *Oli* oliva inferior, *P-cell* Purkinje cell, *vq* ventriculus quartus, *WM* white matter. (After Sidman and Rakic 1982; Hatten et al. 1997; O’Rahilly and Müller 2001; from ten Donkelaar et al. 2003, with permission)

The **histogenesis** of the cerebellum is summarized in Fig. 1.18. The main cell types of the cerebellum arise at different times of development and at different locations. The Purkinje cells and the deep cerebellar nuclei arise from the ventricular zone of the metencephalic alar plates. Bayer et al. (1995) estimated that in man the deep cerebellar nuclei as well as the Purkinje cells are generated from the early fifth to sixth weeks of development. Towards the end of the embryonic period, granule cells are added from the rhombic lip. The **rhombic lip** (*Rautenleiste* of His

1890) is the dorsolateral part of the alar plate, and it forms a proliferative zone along the length of the hindbrain. Cells from its rostral part, the **upper rhombic lip**, reach the superficial part of the cerebellum, and form the **external germinal or granular layer** at the end of the embryonic period. Granule cells that arise from it migrate along the processes of Bergmann glia cells to their deeper, definitive site. Adhesion molecules such as TAG1, L1 and astroctactin play a role in this migration (Hatten et al.

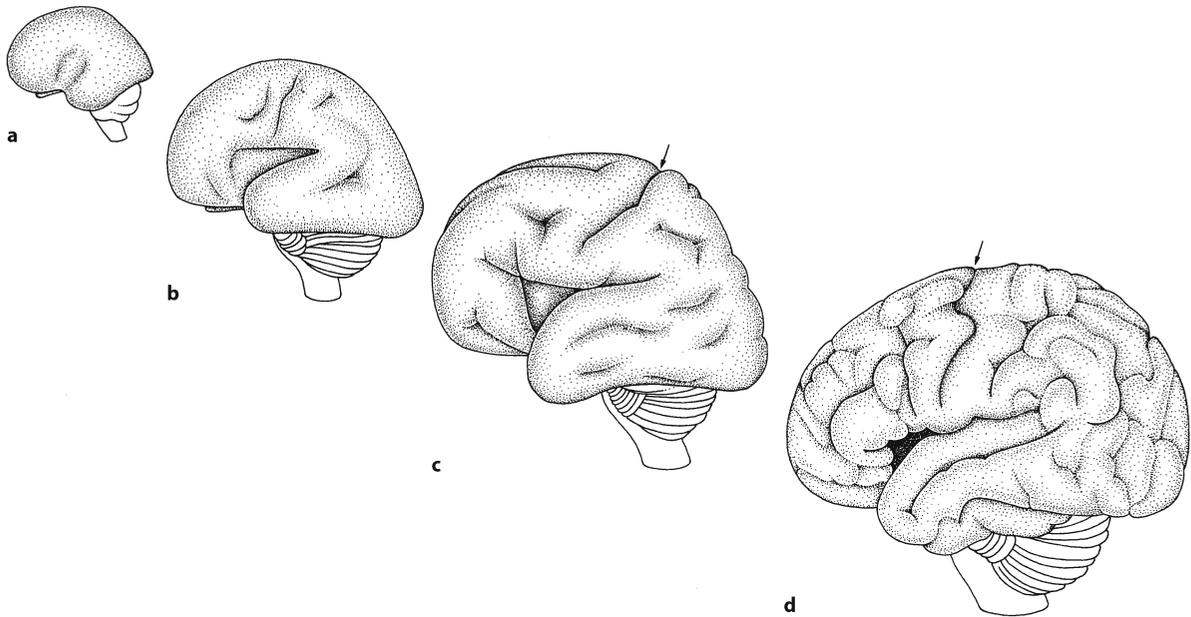


Fig. 1.19 Lateral views of the developing human brain in the fourth (a), sixth (b) and eighth (c) gestational months, and in a neonate (d). The arrows indicate the central sulcus. (After Kahle 1969; O’Rahilly and Müller 1999)

1997). In the fetal period, the **internal granular layer** is formed by further proliferation and migration of the external germinal cells. This layer, situated below the layer of Purkinje cells, is the definitive granular layer of the cerebellar cortex. A transient layer, the **lamina dissecans**, separates the internal granular layer from the Purkinje cells. Ultimately, it is filled by migrating granular cells and disappears (Rakic and Sidman 1970). At the same time as the postmitotic granule cells migrate inwards (16–25 weeks), the Purkinje cells enlarge and develop dendritic trees. In man, the external germinal layer appears at the end of the embryonic period and persists for several months to 1–2 years after birth (Lemire et al. 1975). The caudal part of the rhombic lip, the **lower rhombic lip**, gives rise to the pontine nuclei and the inferior olivary nucleus (Essick 1912; Wingate 2001; Fig. 1.17c). Neurons of these precerebellar nuclei migrate along various pathways, the **corpus pontobulbare** in particular, to their ultimate position in the brain stem (Altman and Bayer 1997).

Several genes have a marked impact upon cerebellar development. In mice, knockouts of the *Wnt1* and *En1* genes largely or totally eliminate the cerebellum, whereas in *En2* knockouts the lobular pattern of the posterior vermis is disrupted (Hatten et al. 1997; Millen et al. 1999; Wang and Zoghbi 2001). The *Math1* (mouse atonal homologue) gene is expressed in the rhombic lip (Ben-Arie et al. 1997). In *Math1* knockout mice, no granular layer is formed. SHH is expressed in migrating and settled Purkinje cells, and

acts as a potent mitogenic signal to expand the granule cell progenitor population (Wechsler-Reya and Scott 1999). **Medulloblastoma**, a brain stem tumour of childhood, is thought to originate in malignant external granule cells. **Developmental malformations** of the cerebellum are mostly bilateral and may be divided into (1) malformations of the vermis and (2) malformations of the vermis as well as of the hemispheres (Norman et al. 1995; Kollias and Ball 1997; Ramaeckers et al. 1997; Barkovich 2000; ten Donkelaar et al. 2003). **Agensis** or **hypoplasia** of the **vermis** may occur in a great variety of disorders, most frequently in the **Dandy–Walker malformation** (Chap. 8). **Pontocerebellar hypoplasia** forms a large group of disorders, characterized by a small pons and a varying degree of hypoplasia of the cerebellum (Barth 1993; Ramaeckers et al. 1997), up to its near-total absence (Gardner et al. 2001).

1.8.2 The Cerebral Cortex

The outgrowth of the **cerebral cortex** and the proliferation and migration of cortical neurons largely takes place in the fetal period. Each hemisphere first grows caudalwards, and then bends to grow in ventral and rostral directions (Figs. 1.19, 1.20). In this way the temporal lobe arises. The outgrowth of the caudate nucleus, the amygdala, the hippocampus and the lateral ventricle occurs in a similar, C-shaped way. During the fetal period, the complex pattern of sulci

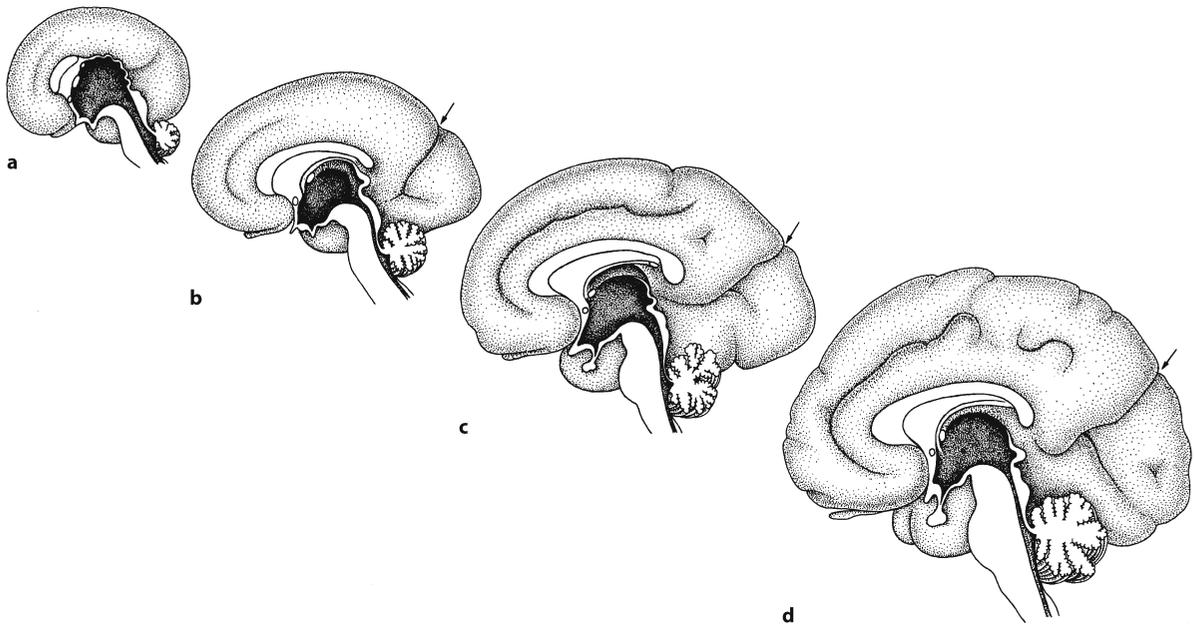


Fig. 1.20 Medial views of the developing human brain at the end of the fourth (a), sixth (b) and eighth (c) gestational months, and in a neonate (d). The arrows indicate the sulcus parieto-occipitalis. (After Macchi 1951, Kahle 1969 and Feess-Higgins and Larroche 1987)

and gyri arises. On the lateral surface of the brain the **sulcus lateralis** and the **sulcus centralis** can be recognized from 4 months onwards. Owing to the development of the prefrontal cortex, the sulcus centralis gradually moves caudalwards. On its medial surface first the parieto-occipital and cingulate sulci appear, followed by the calcarine and central sulci. The formation of sulci and gyri in the right hemisphere usually precedes that in the left one. The **plexus choroideus** of the lateral ventricle arises in the lower part of the medial wall of the telencephalic vesicle (Fig. 1.16).

Usually, the **pallium** is divided into a **medial pallium** or **archipallium**, a **dorsal pallium** or **neopallium** and a **lateral pallium** or **paleopallium** (Fig. 1.21). Recently, an additional **ventral pallium** was added (Puelles et al. 2000; Marín and Rubinstein 2002; Schurmans and Guillemot 2002). The medial pallium forms the hippocampal cortex, the three-layered allocortex. Parts of the surrounding transitional cingulate and entorhinal cortex, the four-to-five-layered mesocortex, may have the same origin. The dorsal pallium forms the six-layered isocortex. The lateral pallium forms the olfactory cortex and the ventral pallium the claustramygdaloid complex. The **subpallium** consists of two progenitor domains, the lat-

eral and medial ganglionic eminences, generating the striatum and the pallidum, respectively. Dorsal and ventral domains of the developing telencephalon are distinguished by distinct patterns of gene expression, reflecting the initial acquisition of regional identity by progenitor populations (Puelles et al. 2000; Schurmans and Guillemot 2002; Chap. 9).

The **hippocampal formation** or **formatio hippocampi** comprises the dentate gyrus, the hippocampus, the subiculum and the parahippocampal gyrus. These structures develop from the medial pallium and are originally adjacent cortical areas (Fig. 1.22). During the outgrowth of the cerebral hemispheres, first caudalwards and subsequently ventralwards and rostralwards, the *retrocommissural part* of the hippocampal formation becomes situated in the temporal lobe (Stephan 1975; Duvernoy 1998). Rudiments of the *supracommissural part* of the hippocampus can be found on the medial side of the hemisphere on top of the corpus callosum: the *indusium griseum*, a thin cell layer, flanked by the *stria longitudinalis medialis* and *lateralis* of Lancisi (Chap. 10). At the beginning of the fetal period, the hippocampal formation contains four layers (Humphrey 1966; Kahle 1969; Arnold and Trojanowski 1996): a ventricular zone, an intermediate layer, a hippocampal plate comprised of

Fig. 1.21 Subdivision of the forebrain into the medial pallium (MP), dorsal pallium (DP), lateral pallium (LP) and ventral pallium (VP), and subpallium. AEP/POA anterior entopeduncular/preoptic area, CH cortical hem, dLGE dorsal part of lateral ganglionic eminence, MGE medial ganglionic eminence, vLGE ventral part of lateral ganglionic eminence. (After Puelles et al. 2000; Schuurmans and Guillemot 2002)

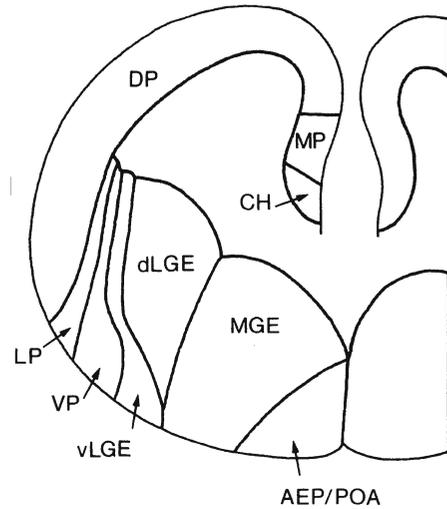
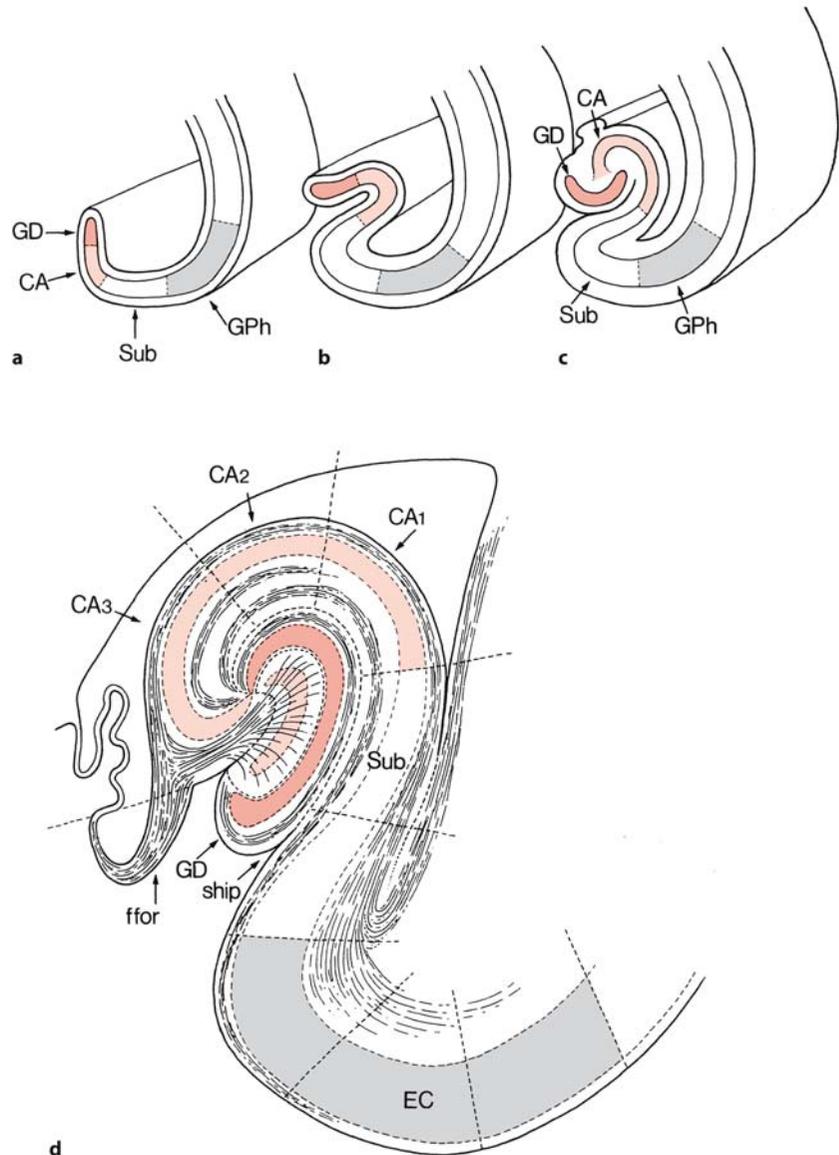


Fig. 1.22 Development (a–c) and structure (d) of the human hippocampal formation. The cornu Ammonis (CA) is indicated in light red, the dentate gyrus (GD) in red and the entorhinal cortex (EC) in grey. CA1–CA3 cornu Ammonis subfields, ffor fimbria fornix, GPh gyrus parahippocampalis, ship sulcus hippocampi, Sub subiculum



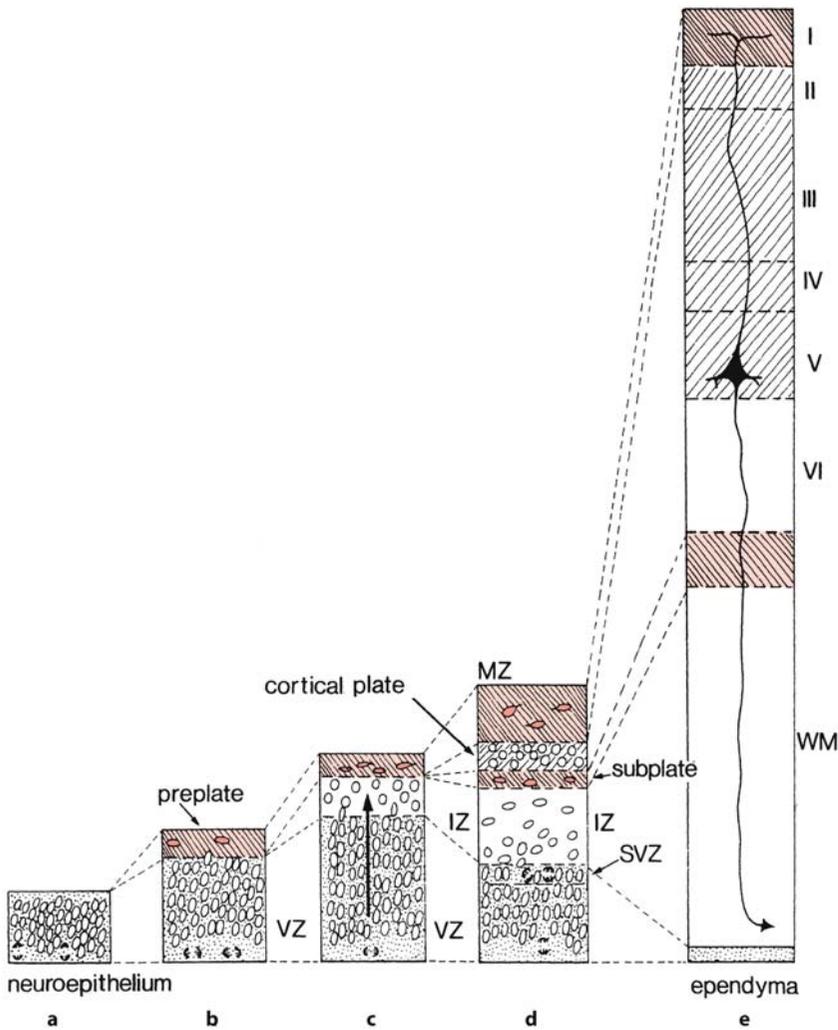


Fig. 1.23 Histogenesis of the cerebral cortex. **a–c** The neuroepithelium forms three zones, the ventricular zone (VZ), the intermediate zone (IZ) and the preplate. During the eighth to 18th weeks of development, neurons migrate from the ventricular zone and form the cortical plate (**d**). The preplate becomes divided into the marginal zone (MZ) and the subplate. A second compartment for cell division, the subventricular zone (SVZ), is mainly involved in the production of glial cells. Finally (**e**), the marginal zone forms the molecular layer (layer I) and the cortical plate layers II–VI. The intermediate zone forms the subcortical white matter (WM). The subplate disappears. (After O’Rahilly and Müller 1999)

bipolar-shaped neurons, and a marginal zone. At 15–19 weeks of gestation, individual subfields can be distinguished. A distal-to-proximal gradient of cytoarchitectonic and neuronal maturity is found, with the subiculum appearing more developed than the ammonic subfields (CA1–CA3). The dentate gyrus is the latest area to develop. Most pyramidal cells in the cornu Ammonis fields are generated in the first half of pregnancy and no pyramidal neurons are formed after the 24th gestational week (Seress et al. 2001). Granule cells of the dentate gyrus proliferate at a decreasing rate during the second half of pregnancy and after birth but still occur at a low percentage during the first postnatal year (Seress et al. 2001). Reciprocal entorhinal–hippocampal connections are established by fetal midgestation (Hevner and Kinney 1996). Fibres connecting the entorhinal cortex, hippocampus and subiculum are present by about 19 weeks of gestation. The perforant path, connecting the entorhinal cortex with the dentate gyrus, and all

connections with the neocortex are only beginning at 22 weeks of gestation.

The **histogenesis** of the six-layered cerebral cortex is shown in Fig. 1.23. The developing cerebral wall contains several transient embryonic zones: (1) the ventricular zone, which is composed of dividing neural progenitor cells; (2) the subventricular zone, which acts early in corticogenesis as a secondary neuronal progenitor compartment and later in development as the major source of glial cells; (3) the intermediate zone, through which migrating neurons traverse along radial glial processes; (4) the subplate, thought to be essential in orchestrating thalamocortical connectivity and pioneering corticofugal projections (Chap. 2); (5) the cortical plate, the initial condensation of postmitotic neurons that will become layers II–VI of the mature cortex; and (6) the marginal zone, the superficial, cell-sparse layer that is important in the establishment of the laminar organization of the cortex.

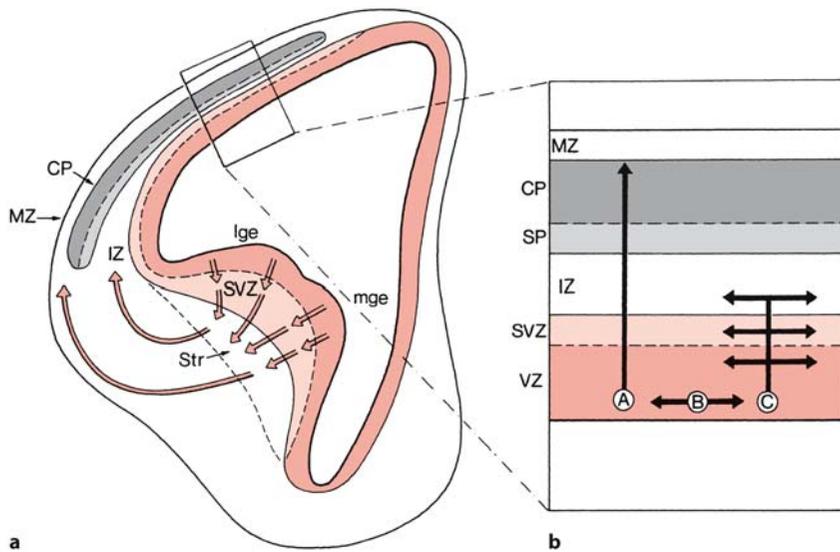


Fig. 1.24 Radial and tangential migration of cortical neurons. **a** The proliferative compartments of the murine telencephalon: the ventricular zone (VZ, red) and the subventricular zone (SVZ, light red). Postmitotic GABAergic neurons leave the lateral (*lge*) and medial (*mge*) ganglionic eminences and reach the striatum (*Str*) and through tangential migration the

marginal zone (MZ) and the intermediate zone (IZ). **b** Part of the cortex is enlarged in which radial migration of neurons (A) through the subplate (SP) to the cortical plate (CP) and tangential migration, occurring in the ventricular, subventricular and intermediate zones (B, C), is indicated. (After Pearlman et al. 1998)

Cortical neurons are generated in the ventricular zones of the cortical walls and ganglionic eminences, and reach their destination by radial and tangential migration, respectively. The first postmitotic cells form the **preplate** or **primordial plexiform layer** (Marín-Padilla 1998; Meyer and Goffinet 1998; Supèr et al. 1998; Zecevic et al. 1999; Meyer et al. 2000). Then, cells from the ventricular zone migrate to form an **intermediate zone** and, towards the end of the embryonic period, the **cortical plate**. This plate develops within the preplate, thereby dividing the preplate into a minor superficial component, the **marginal zone** and a large deep component, the **subplate**. The marginal zone is composed largely of **Cajal–Retzius neurons** (Meyer et al. 1999), secreting the extracellular protein Reelin, and the subplate contains pioneer projection neurons. Reelin is required for the normal inside-to-outside positioning of cells as they migrate from the ventricular zone. The formation of the cortical plate takes place from approximately 7 to 16 weeks. The first cells to arrive will reside in the future layer VI. Cells born later migrate past the already present cortical cells to reside in progressively more superficial layers. In this way, cortical layers VI–II are subsequently formed. The marginal zone becomes layer I, i.e. the molecular or plexiform layer. The subplate gradually disappears. The ventricular zone becomes the ependyma and the intermediate zone

the subcortical white matter. A transient cell layer, the **subpial granular layer** (SGL) of Ranke (1910), originates from the basal periofactory subventricular zone (Brun 1965; Gadisseux et al. 1992; Meyer and Wahle 1999). It migrates tangentially beneath the pia to cover the neocortical marginal zone from the 14th gestational week onwards. The SGL provides a constant supply of Reelin-producing cells during the critical period of cortical migration, keeping pace with the dramatic growth and surface expansion during corticogenesis. Naturally occurring cell death is an active mechanism contributing to the disappearance of the SGL (Spreatico et al. 1999).

In the telencephalon, **radial migration** is the primary mechanism by which developing neurons arrive at their final position (Rakic 1972). The newly born neuroblasts associate with specialized glial cells known as the radial glial cells. Radial glial cells are bipolar cells with one short process extended to the adjacent ventricular surface and a second projecting to the pial surface (Chap. 2). A two-way signalling process between the migrating neuron and the radial glial fibre permits the neuroblast to migrate, and provides a signal to maintain the structure of the radial glial fibre (Hatten 1999). This process requires known receptors and ligands such as neuregulin and Erb4, cell adhesion molecules, putative ligands with unknown receptors such as astrotactin, and extracellu-

lar matrix molecules and their surface receptors. Blocking any of these components can slow or prevent radial cell migration (Pilz et al. 2002). Cell migration perpendicular to the radial axis, i.e. **tangential migration** (Fig. 1.24), differs from radial cell migration in the direction of movement and in the mechanism of cell guidance. Instead of radial glia, axons appear to be the substrate for at least some non-radial cell migration (Pearlman et al. 1998). Non-radial cell migration provides most, if not all, GABAergic interneurons of the cerebral cortex. This population of cortical neurons migrates from the ganglionic eminences along non-radial routes to reach the cerebral cortex (Anderson et al. 1999, 2001; Lavdas et al. 1999; Marín and Rubinstein 2001). The medial ganglionic eminence is the source of most cortical interneurons, and is also a major source of striatal interneurons (Marín et al. 2000). The tangential migration of postmitotic interneurons from the ganglionic eminences to the neocortex occurs along multiple paths, and is directed in part by members of the Slit and semaphorin families of guidance molecules (Marín et al. 2001).

Malformation of cortical development may be divided into several categories, based on the stage of development (cell proliferation, neuronal migration, cortical organization) at which cortical development was first affected (Barkovich et al. 2001; Chap. 10). Malformations due to abnormal proliferation or apoptosis may lead to extreme microcephaly. Malformations due to abnormal migration, i.e. **neuronal migration disorders (NMDs)** have been extensively studied (Gleeson and Walsh 2000; Barkovich et al. 2001; Olson and Walsh 2002; Pilz et al. 2002). Malformations due to abnormal cortical organization include the polymicrogyrias and schizencephalies (Barkovich et al. 2001).

The **olfactory bulbs** evaginate after olfactory fibres penetrate the cerebral wall at the ventrorostral part of the hemispheric vesicles (Pearson 1941). By the end of the sixth week, several bundles of fibres arising in the olfactory placodes have reached the forebrain vesicles. A few days later, a shallow protrusion appears at the site of contact, and between 8 and 13 weeks, the cavity of the evagination enlarges and becomes the olfactory ventricle. The olfactory bulbs gradually elongate rostralwards along the base of the telencephalon. Mitral cells arise from the surrounding ventricular zone. As the olfactory bulbs form, future granule and preglomerular cells are generated in the subventricular zone of the lateral ganglionic eminences, and migrate into each bulb along a rostral migratory stream (Hatten 1999). These neurons move rapidly along one another in chain formations, independent of radial glia or axonal processes. In rats and primates, this migration persists into adulthood

(Doetsch et al. 1997; Kornack and Rakic 2001; Brazel et al. 2003). Numerous cells of the **piriform cortex** originate in a region close to the corticostriatal boundary (Bayer and Altman 1991). They reach the rostromedial telencephalon via a lateral cortical stream (de Carlos et al. 1996).

1.8.3 Cerebral Commissures

Cerebral commissures arise in a thin plate, the **embryonic lamina terminalis**, i.e. the median wall of the telencephalon rostral to the chiasmatic plate. It is also known as the lamina reuniens or *Schlussplatte* (His 1889, 1904; Hochstetter 1919; Rakic and Yakovlev 1968). At approximately 5 weeks (stage 16), the **commissural plate** appears as a thickening in the embryonic lamina terminalis. The remainder of the lamina then constitutes the adult lamina terminalis (*Endplatte* of His 1889, 1904). The commissural plate gives rise to (Fig. 1.25) (1) the anterior commissure, which appears at the end of the embryonic period and connects the future temporal lobes, (2) the hippocampal commissure, which appears several weeks later and connects the crura of the fornix, and (3) the corpus callosum, which appears early in the fetal period and connects the cerebral hemispheres. The **corpus callosum** is first identified at 11–12 weeks after ovulation, and gradually extends considerably caudalwards. The overlying part of the commissural plate becomes thinned to form the septum pellucidum. Within the septum a narrow cavity appears, the cavum septi pellucidi. The corpus callosum appears to be fully formed by the middle of prenatal life. Partial or complete **absence** of the **corpus callosum** is not uncommon (Aicardi 1992; Norman et al. 1995; Kollias and Ball 1997; Barkovich 2000). Every disorder that influences the development of the commissural plate may lead to this malformation. Dysgenesis of the corpus callosum occurs in approximately 20% of cases as an isolated disorder, but in about 80% of cases in combination with other disorders of the brain (Chap. 10).

1.8.4 Imaging of the Fetal Brain

Fetal magnetic resonance images at 20 and 35 weeks of development are shown in Figs. 1.26 and 1.27, respectively. At 20 weeks of development, cortical layers, the hypodense subplate in particular, can be easily distinguished in the smooth cerebral cortex. Germinal zones are hyperdense. A 35-week-old brain shows the extensive changes that appear in the cerebrum in the second half of pregnancy. Garell's (2004) MRI atlas presents the fetal brain in detail from 20 weeks of development until birth.

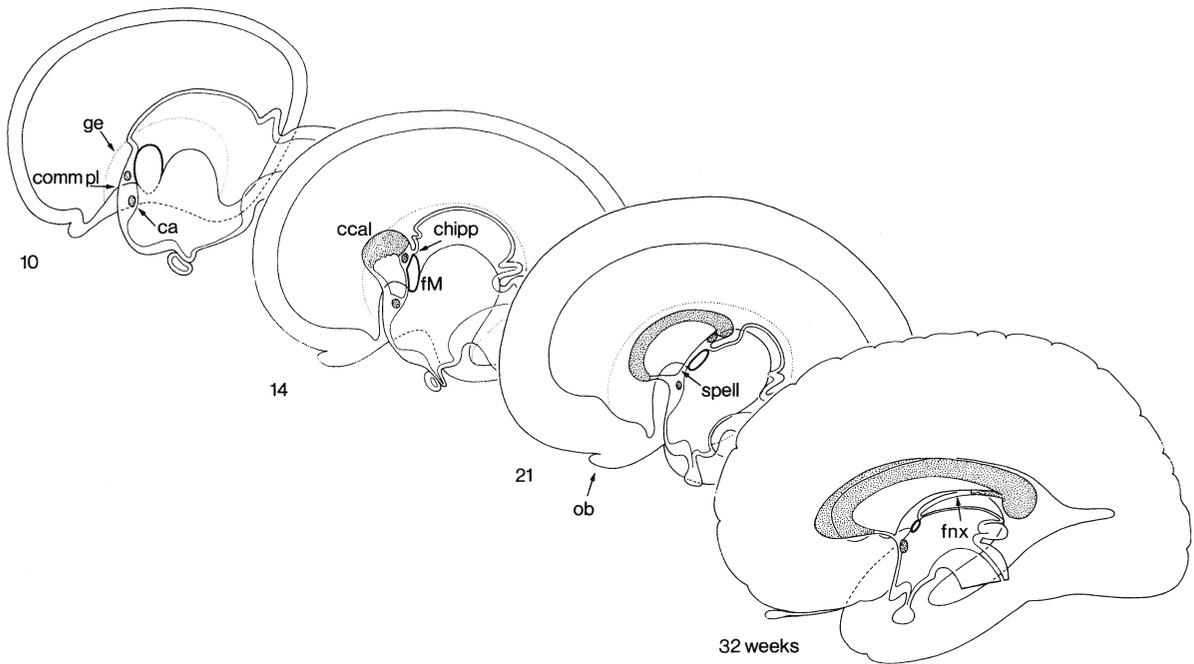


Fig. 1.25 Development of the cerebral commissures at the 10th, 14th, 21st and 32rd weeks of development. *ca* commissura anterior, *ccal* corpus callosum, *chipp* commissura hip-

pocampi, *comm pl* commissural plate, *fM* foramen of Monro, *fnx* fornix, *ge* ganglionic eminence, *ob* olfactory bulb, *spell* septum pellucidum. (After Streeter 1911, 1912)

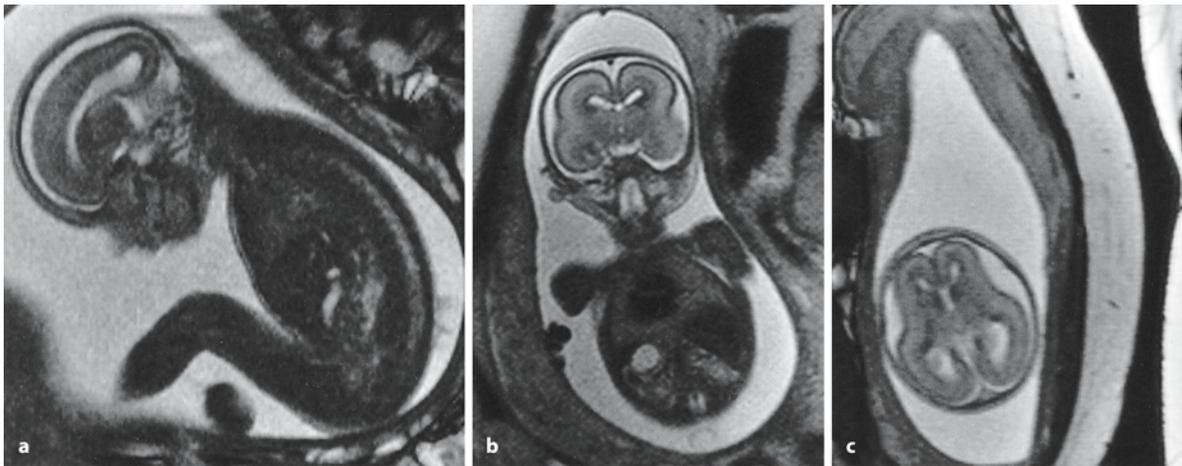


Fig. 1.26 Fetal T2-weighted MRI taken at the 20th week of development: **a** sagittal section; **b** frontal (or coronal) section; and **c** horizontal (or axial) section. There is a smooth cerebral

surface without gyration. The thick periventricular germinal layer has a low-signal intensity. A thin cortical layer is present, below which the large subplate can be recognized

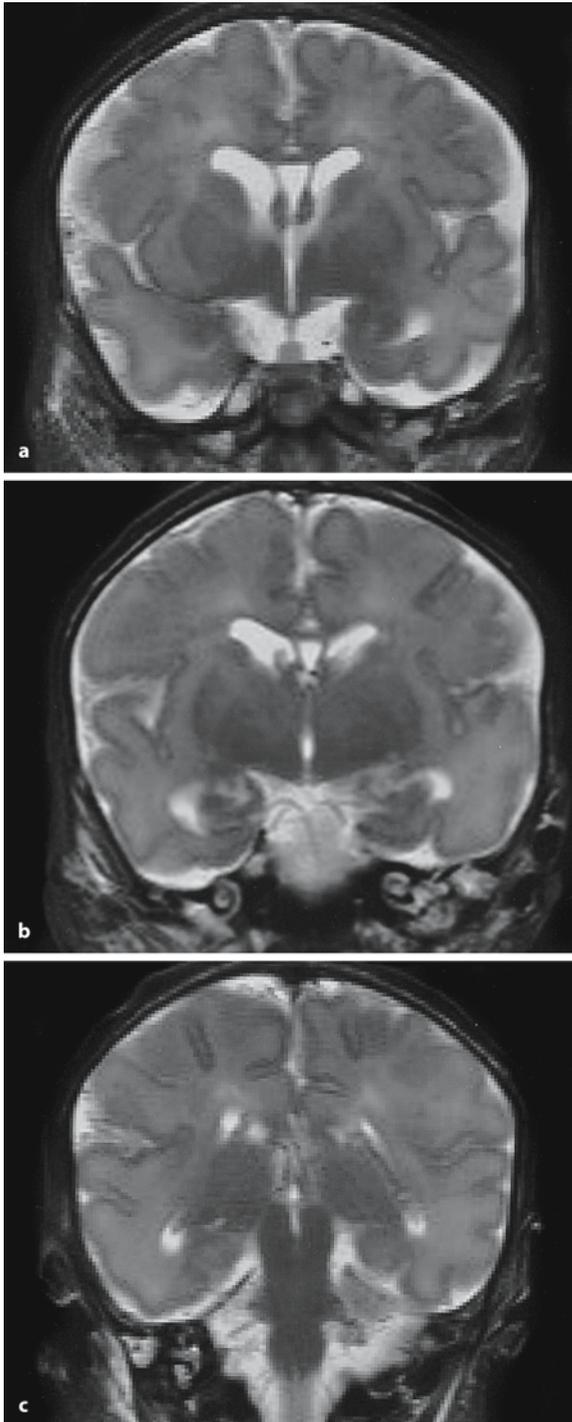


Fig. 1.27 Fetal T2-weighted MRI taken at the 35th week of development. The three frontal (or coronal) sections show increasing development of the insulae and lateral fissures, and an increasing number of gyri and sulci. The basal ganglia (in **a**), the amygdala (in **a**) and the hippocampal region (in **b**) are easily recognized. Note the large cavum septi pellucidum and the prominent fornices (in **a** and **b**). The corpus callosum is visible in **a** and **b**

1.9 Development of the Meninges and Choroid Plexuses

The **cranial meninges** originate from several sources such as the prechordal plate, the parachordal mesoderm and the neural crest (O’Rahilly and Müller 1986). The loose mesenchyme around most of the brain at 5 weeks of development (stage 15) forms the primary meninx. At 6 weeks (stage 17), the dural limiting layer is found basally and the skeletogenous layer of the head becomes visible. At 7 weeks (stage 19), the cranial pachymeninx and leptomeninx are distinguishable. Hochstetter (1939) showed that, as the dural reflections develop, the posterior point of attachment between the tentorium cerebelli and the falx cerebri gradually moves to a more caudal position in the skull, thereby producing a continual reduction in the size of the posterior cranial fossa relative to that of the supratentorial fossae. Increases of supratentorial volume relative to infratentorial volume affect such an inferoposterior rotation of the human fetal tentorium cerebelli (Jeffery 2002). Klintworth (1967) found the tentorium cerebelli at stage 20 as a bilateral, three-layered structure. The two tentorial precursors were visible macroscopically by stage 23. They fuse at 55-mm crown–rump length (CRL) to create the straight sinus (Streeter 1915).

The development of the **spinal meninges** has been studied by Hochstetter (1934) and Sensenig (1951). The future pia mater appears as neural crest cells by stage 11, and at 5 weeks (stage 15) the primary meninx is represented by a loose zone between the developing vertebrae and the neural tube. After 6 weeks (stage 18), the mesenchyme adjacent to the vertebrae becomes condensed to form the dural lamella. At the end of the embryonic period (stage 23), the dura completely lines the wall of the vertebral canal. The spinal arachnoid, however, does not appear until either the third trimester or postnatally (O’Rahilly and Müller 1999).

A **choroid plexus** first appears in the roof of the fourth ventricle at stage 18, in the lateral ventricles at stage 19, and in the third ventricle at stage 21 (Ariëns Kappers 1958; Bartelmez and Dekaban 1962). The primordia appear as simple or club-shaped folds protruding into the ventricles. During stage 21, the choroid plexuses become vascularized. The early choroid plexus of the lateral ventricle is lobulated with vessels running in the mesenchymal stroma and forming capillary nets within the single-layered ependyma. The embryonic choroid plexus is converted into the fetal type during the ninth week of development as the embryonic capillary net is replaced by elongated loops of wavy capillaries that lie under regular longitudinal epithelial folds (Kraus and Jirásek 2002). The stroma of the plexus originates from ex-

tensions of the arachnoid into the interior of the brain that form the **vela interposita**. This may explain the origin of the sporadically occurring intraventricular meningiomas, most commonly found in the trigone of the third ventricle (Nakamura et al. 2003).

1.10 Development of the Blood Supply of the Brain

The brain is supplied by two pairs of internal carotid and vertebral arteries, connected by the circle of Willis. During the closure of the neural tube, primordial endothelial blood-containing channels are established. From these all other vessels, arteries, veins and capillaries are derived. At stage 12, capital venous plexuses, the capital vein and three aortic arches are present (Streeter 1918; Congdon 1922; Padget 1948, 1957; Fig. 1.28). The internal carotids develop early (stages 11–13), followed by the posterior communicating artery, the caudal branch of the internal carotid at stage 14, the basilar and vertebral arteries (stage 16), the main cerebral arteries (stage 17) and finally the anterior communicating artery, thereby completing the circle of Willis (Evans 1911, 1912; Padget 1948; Gillilan 1972). Bilaterally, longitudinal arteries are established at stage 13 and are connected with the internal carotids by temporary trigeminal, otic and hypoglossal arteries. At first, the posterior communicating artery provides the major blood supply of the brain stem. Anastomotic channels unite the two longitudinal arteries, thereby initiating the formation of the basilar artery. The temporary arteries are gradually eliminated, but each of them may persist. The primitive trigeminal artery is the most common of the primitive carotid–basilar anastomoses that persist into adulthood, with an incidence of 0.1–1.0% (Wollschlaeger and Wollschlaeger 1964; Lie 1968; Salas et al. 1998; Suttner et al. 2000; Fig. 1.29). The persistence of a primitive otic artery is shown in Fig. 1.30.

Capillaries at the level of the cerebral hemispheres begin to appear at 5 weeks, and probably earlier in the brain stem (Padget 1948; O’Rahilly and Müller 1999). By 5 weeks (stage 16), many of the definitive arteries are present and are being transformed into the definitive pattern. At the end of the embryonic period, an anular network of **leptomeningeal arteries** arises from each middle cerebral artery and extends over each developing hemisphere (Van den Bergh and Vander Eecken 1968). Similar meningeal branches, originating from the vertebral and basilar arteries, embrace the brain stem and cerebellum. From these gradually muscularizing leptomeningeal artery branches grow into the brain. Both supratentorially and infratentorially, **paramedian, short circumferential and long circumferential arteries** can be distin-

guished. The first vessels penetrate the telencephalon in the seventh week of gestation, form a subventricular plexus at about 12 weeks of gestation (Duckett 1971) and also gradually muscularize. The paramedian branches of the anterior cerebral artery have a short course before they penetrate the cerebral parenchyma, whereas the short circumferential arteries such as the striate artery have a slightly longer course and the long circumferential arteries may reach the dorsal surface of the cerebral hemispheres. At 16 weeks of gestation, the anterior, middle and posterior cerebral arteries, contributing to the formation of the circle of Willis, are well established (Padget 1948; Van den Bergh and Vander Eecken 1968). During the further fetal period the relatively simple leptomeningeal arteries increase in tortuosity, size and number of branches. Their branching pattern is completed by 28 weeks of gestation (Takashima and Tanaka 1978).

The leptomeningeal perforating branches pass into the cerebral parenchyma as **cortical, medullary and striate branches** (Fig. 1.31). The cortical vessels supply the cortex via short branches, whereas the medullary branches supply the underlying white matter. The striate branches penetrate into the brain via the anterior perforate substance and supply the basal ganglia and internal capsule. The cortical and medullary branches supply cone-shaped areas along the periphery of the cerebrum and are called **ventriculopetal arteries**. Striate branches arborize close to the ventricle and supply a more central part of the cerebrum. Together with branches of the tela choroidea, they were supposed to give rise to **ventriculofugal arteries**, supplying the ventricular zone or germinal matrix (Van den Bergh and Vander Eecken 1968; De Reuck et al. 1972). The presence of such arteries could not be confirmed by Gilles and co-workers (Kuban and Gilles 1985; Nelson et al. 1991). More likely, the central parts are supplied by deep penetrating branches (Rorke 1982). Smooth muscle is present at the basal ends of striatal arteries by midgestation and extends well into the vessels in the caudate nucleus by the end of the second trimester (Kuban and Gilles 1985). The intracortical vessels also develop gradually (Allsop and Gamble 1979). From the 13th to 15th weeks, radial arteries without side branches course through the cortex. By 20 weeks of gestation, horizontal side branches and recurrent collaterals appear, and from 27 weeks to term, shorter radial arteries increase in number. Growth of the intracortical capillaries continues well after birth (Norman and O’Kusky 1986). In the fetal brain, the density of capillaries is much higher in the ventricular zone than in the cortical plate until 17 weeks (Duckett 1971; Allsop and Gamble 1979; Norman and O’Kusky 1986). After 25 weeks, increasing vascularization of the cortical areas occurs.

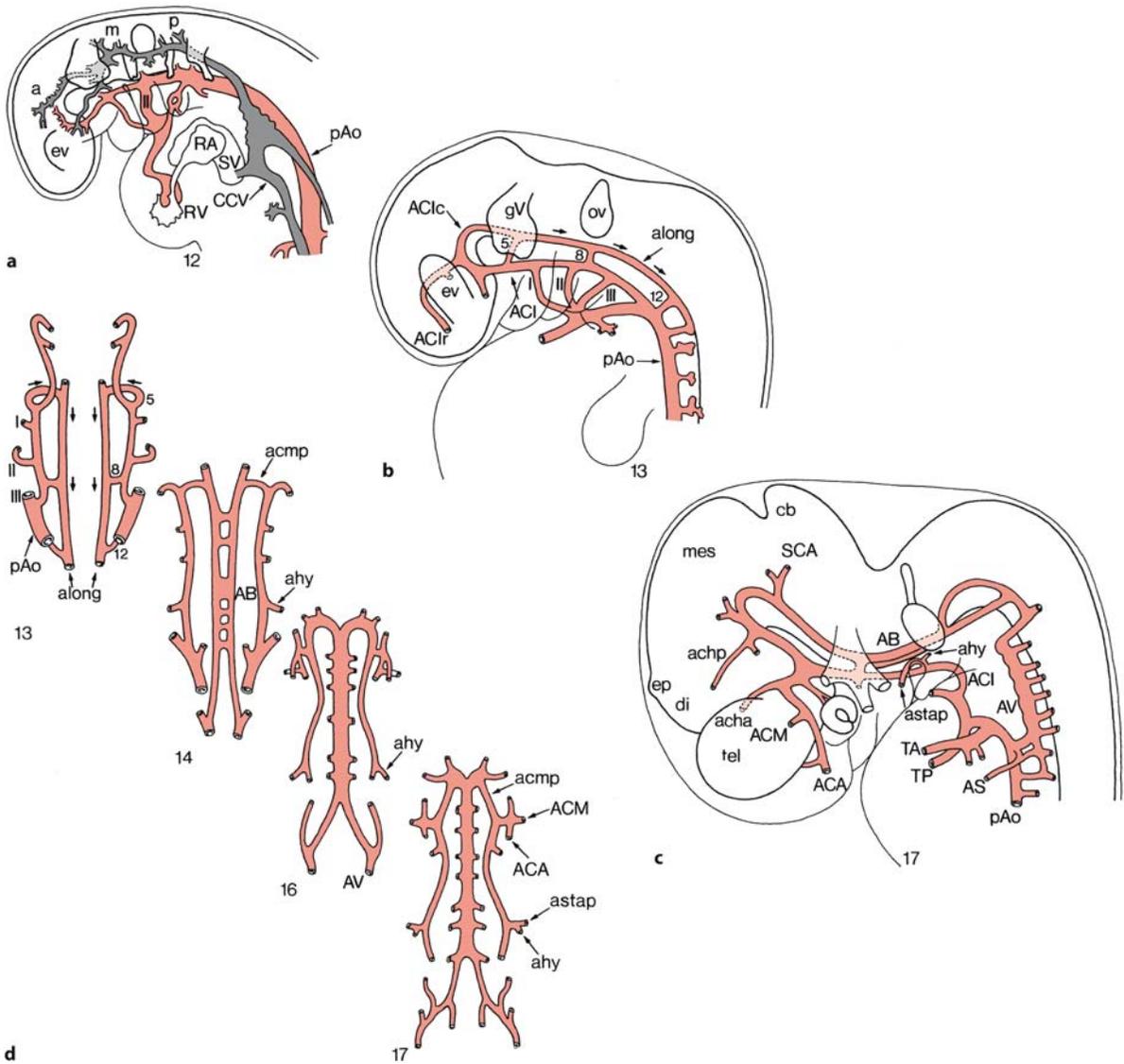


Fig. 1.28 Overview of the development of the blood supply of the human brain from stage 12 until the neonatal period. Arteries are in red, veins in grey. *a* anterior capital plexus, *AA* aortic arch, *AB* a. basilaris, *ACA* a. cerebri anterior, *ACE* a. carotis externa, *acha* anterior choroidal artery, *achp* posterior choroidal artery, *ACI* a. carotis interna, *ACIc* caudal branch of a. carotis interna, *ACIr* rostral branch of a. carotis interna, *ACM* a. cerebri media, *acmp* a. communicans posterior, *ACP* a. cerebri posterior, *ahy* hyoid artery, *AICA* anterior inferior cerebellar artery, *along* a. longitudinalis, *AS* a. subclavia, *astap* a. stapedia, *AV* a. vertebralis, *cb* cerebellum, *cc* corpus callosum, *CCV* com-

mon cardinal vein, *DA* ductus arteriosus, *di* diencephalon, *ep* epiphysis, *ev* eye vesicle, *gV* trigeminal ganglion, *m* middle capital plexus, *OA* ophthalmic artery, *ov* otic vesicle, *p* posterior capital plexus, *pAo* posterior aorta, *PICA* posterior inferior artery, *plch* plexus choroideus, *RA* right atrium, *RV* right ventricle, *SCA* superior cerebellar artery, *SV* sinus venosus, *TA* truncus arteriosus, *tel* telencephalon, *TP* truncus pulmonalis, *I-III* aortic branches, *5, 8, 12* temporary trigeminal, otic and hypoglossal arteries. (After Padget 1948; O’Rahilly and Müller 1999)

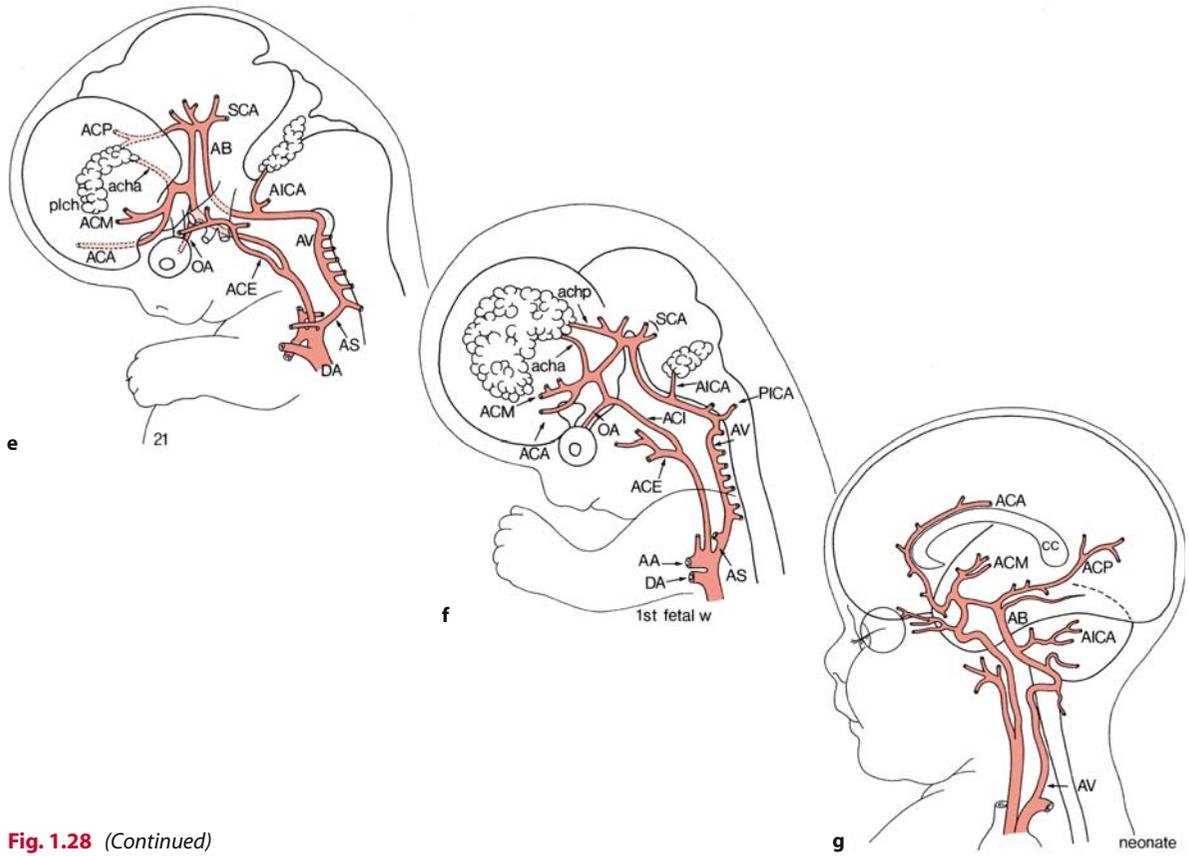
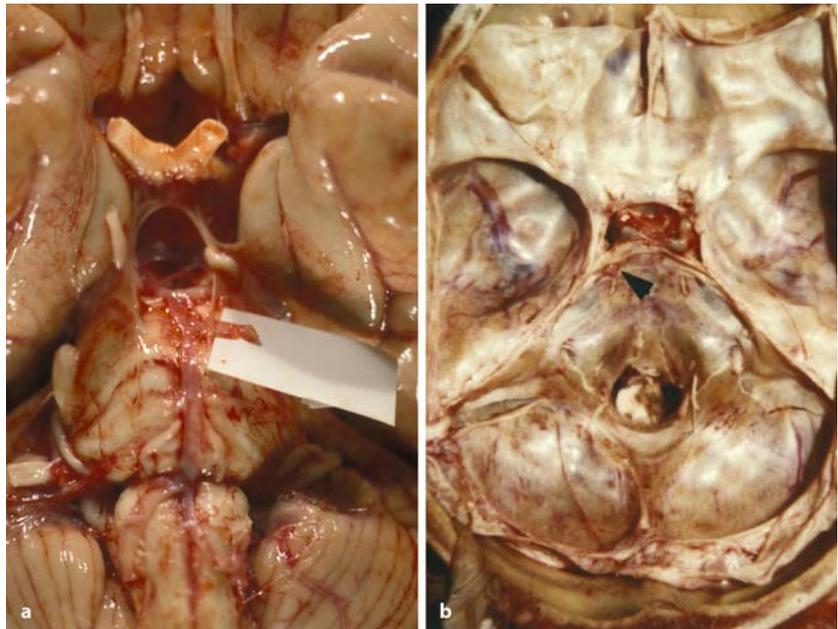


Fig. 1.28 (Continued)

Fig. 1.29 Persistence of the primitive trigeminal artery. Occasional autopsy finding by Akira Hori in a 42-year-old woman



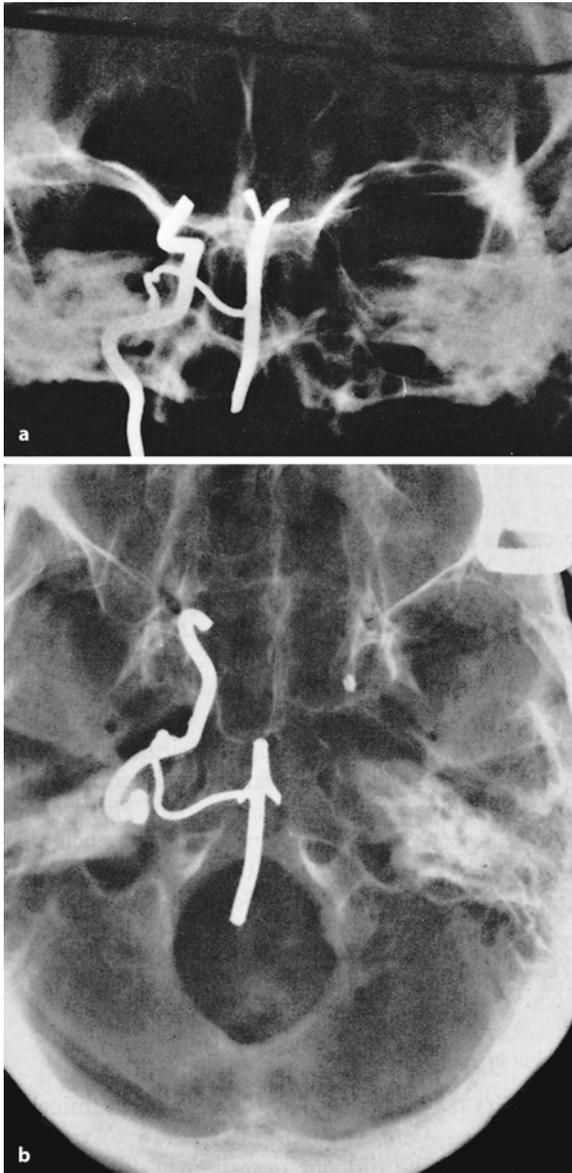


Fig. 1.30 Persistence of the primitive otic artery (from Lie 1968)

At 24 weeks of gestation, a large part of the basal ganglia and internal capsule is supplied by a prominent **Heubner's artery**, arising from the anterior cerebral artery (Hambleton and Wigglesworth 1976). The capillary bed in the ventricular zone is supplied mainly by Heubner's artery and terminal branches of the lateral striate arteries from the middle cerebral artery (Wigglesworth and Pape 1980). The cortex and the underlying white matter are rather poorly vascularized at this stage of development. Gradually, the area supplied by the middle cerebral artery becomes predominant when compared with the territories supplied by the anterior and posterior cerebral arter-

ies (Okudera et al. 1988). Early arterial anastomoses appear around 16 weeks of gestation. The sites of arterial anastomoses between the middle and the anterior cerebral arteries move from the convexity of the brain towards the superior sagittal sinus and those between the middle and posterior cerebral arteries move towards the basal aspect of the brain. By 32–34 weeks of gestation, the ventricular zone involutes and the cerebral cortex acquires its complex gyral pattern with an increased vascular supply. The ventricular zone capillaries blend with the capillaries of the caudate nucleus and the territory of Heubner's artery becomes reduced to only a small medial part of the caudate nucleus. In the cortex, there is progressive elaboration of the cortical blood vessels (Van den Bergh and Vander Eecken 1968; Hambleton and Wigglesworth 1976; Weindling 2002). Towards the end of the third trimester, the balance of cerebral circulation shifts from a central, ventricular zone oriented circulation to a circulation predominant in the cerebral cortex and white matter. These changes in the pattern of cerebral circulation are of major importance in the pathogenesis and distribution of hypoxic/ischemic lesions in the developing human brain.

Cerebrovascular density correlates with regional metabolic demand (Pearce 2002). Correspondingly, cerebrovascular conductance in the vertebrobasilar and carotid systems increases more slowly than brain weight, particularly during the postnatal period of rapid cerebral growth, myelination and differentiation. As part of normal development, most immature human cerebral arteries appear to have regions of weakened media near vessel bifurcations. These weakened areas are reinforced during maturation via the deposition of additional smooth muscle, but can comprise areas of heightened vulnerability to rupture during early postnatal development (Pearce 2002).

In younger premature infants (22–30 weeks old), the blood vessels of the germinal, periventricular zone and the perforating ventriculopetal vessels are particularly vulnerable to *perinatal asphyxia* (Marín-Padilla 1996; Volpe 1998; Weindling 2002). Damage to these vessels often causes focal haemorrhagic lesions. In older premature infants (30–34 weeks), the fetal white matter seems to be particularly vulnerable to hypoxic-ischemic injury, leading to *periventricular leukomalacia* or *PVL* (Chap. 3), and often resulting in infarction (necrosis) and cavitation (Banker and Larroche 1962; Marín-Padilla 1997, 1999; Volpe 2001; Squier 2002; Weindling 2002). PVL refers to necrosis of white matter in a characteristic distribution, i.e. in the white matter dorsal and lateral to the external angles of the lateral ventricles. The corticospinal tracts run through the periventricular region. Therefore, impaired motor function is

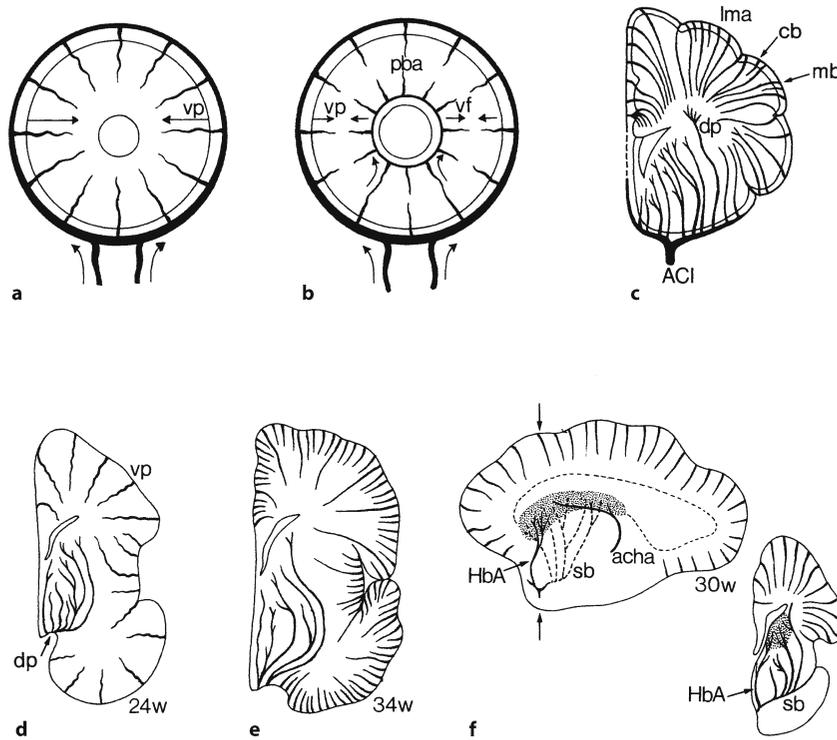


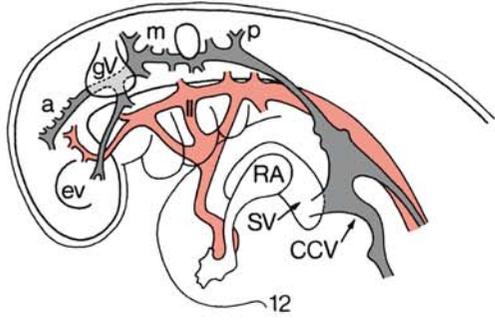
Fig. 1.31 Development of cerebral blood vessels. The brain is surrounded by a system of leptomeningeal arteries, which is supplied by afferent trunks at the base of the brain, and gives off ventriculopetal arteries (*vp*) towards the lateral ventricle (a). A few deep-penetrating arteries supply periventricular parts of the brain and were supposed to send ventriculofugal arteries (*vf*) towards the ventriculopetal vessels, without making anastomoses (b). Between these two systems there may be a periventricular border area. Deep penetrators (*dp*) more likely supply the periventricular parts of the brain. c The

arrangement of both types of vessels around a cerebral hemisphere. d, e Changes in the arterial pattern of the cerebrum between 24 and 34 weeks of gestation. f Blood supply to the basal ganglia at 20 weeks of gestation. *acha* anterior choroidal artery, *ACI* internal carotid artery, *cb* cortical branches, *HbA* Heubner's artery, *lma* leptomeningeal arteries, *mb* medullary branches, *pba* periventricular border area, *sb* striate branches of middle cerebral artery. (After Van den Bergh and Vander Eecken 1968; Hambleton and Wigglesworth 1976)

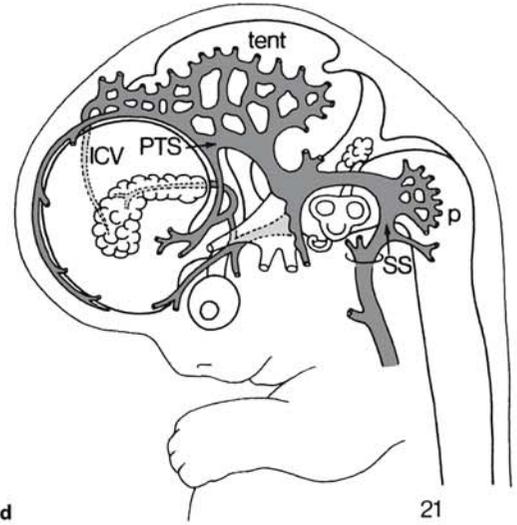
the most common neurologic sequela of periventricular white matter injury (Banker and Larroche 1962; Aida et al. 1998; Staudt et al. 2000). Periventricular white matter lesions account for the pathogenesis of a large number of children with spastic hemiparesis (Niemann et al. 1994).

Dural plexuses associated with the precardinal veins become modified to form the various dural sinuses around the brain (Streeter 1915, 1918; Lindenberg 1956; Padget 1957). Definitive venous channels emerge from the primitive vascular net later than the arteries do. Moreover, the complicated venous anastomoses are essential to facilitate a greater adjustment over a considerably longer period (Padget 1957). The development of the human **cranial venous system** is summarized in Fig. 1.32. During Padget's venous stage 1 (Carnegie stage 12), **capital venous plexuses** and the **capital vein** are forming (Fig. 1.32a). By

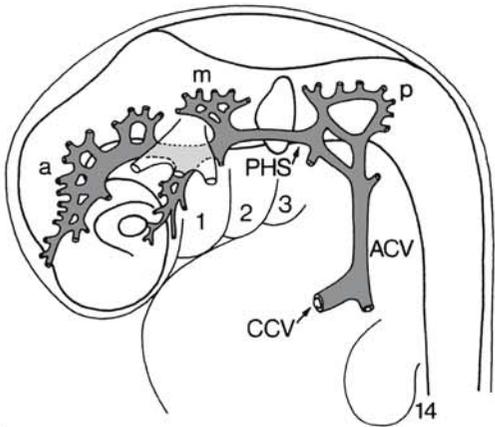
venous stage 2 (Carnegie stage 14), three relatively constant **dural stems**, anterior, middle and posterior, are present draining into a **primary head sinus** (capital or 'head' vein) that is continuous with the anterior cardinal vein. During venous stages 3 and 4 (Carnegie stages 16 and 17), the dural venous channels come to lie more laterally as the cerebral hemispheres and the cerebellar anlage expand and the otic vesicles enlarge (Fig. 1.32c). The head sinus and the primitive internal jugular vein also migrate laterally. By venous stage 5 (Carnegie stage 19), the head sinus is replaced by a secondary anastomosis, the **sigmoid sinus**. Moreover, more cranially the **primitive transverse sinus** is formed. During venous stage 6 (Carnegie stage 21), the external jugular system arises (Fig. 1.32d). Most parts of the brain, except for the medulla, drain into the junction of the sigmoid sinus with the primitive transverse sinus. Meanwhile, the Galenic system of intracerebral drainage emerges as



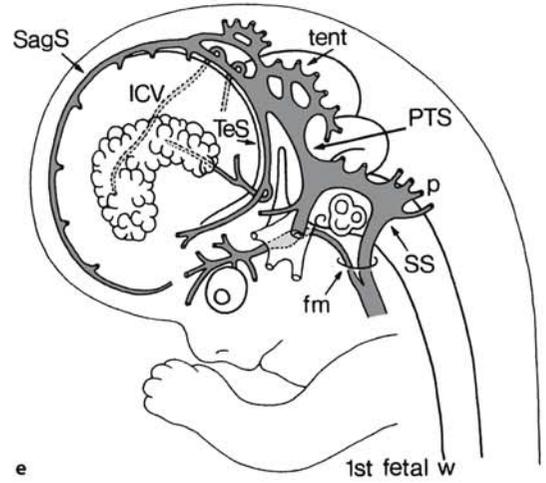
a



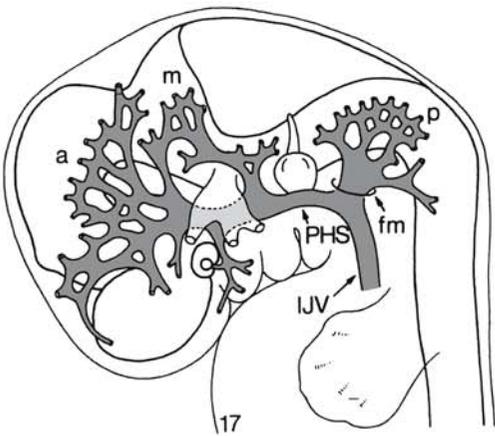
d



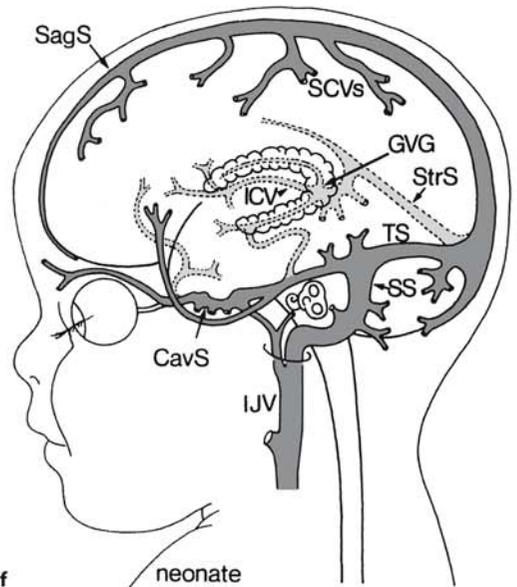
b



e



c



f

Fig. 1.32 Development of the venous system of the human brain from stage 12 until the neonatal period. Veins are in grey, early arteries in red. *a* anterior capital plexus, *ACV* anterior cardinal vein, *CavS* cavernous sinus, *CCV* common cardinal vein, *ev* eye vesicle, *fm* foramen magnum, *GVG* great vein of Galen, *ICV* internal cerebral vein, *IJV* internal jugular vein, *m* middle capital plexus, *p* posterior capital plexus, *PHS* primary head sinus, *PTS* primitive transverse sinus, *RA* right atrium, *SagS* sagittal sinus, *SCVs* superior cerebral veins, *SS* sigmoid sinus, *StrS* straight sinus, *SV* sinus venosus, *tent* tentorial plexus, *TeS* tentorial sinus, *TS* transverse sinus, *II* second aortic branch 1, 2, 3 pharyngeal arches. (After Streeter 1918; Padgett 1957)

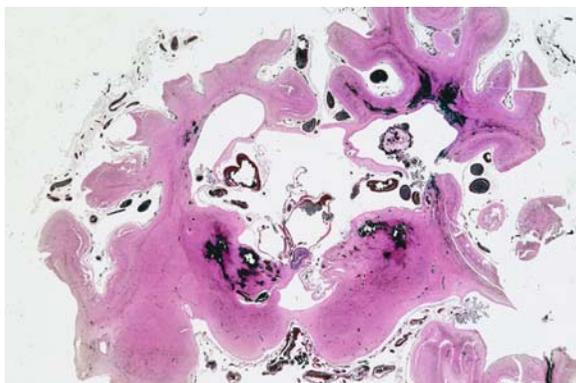


Fig. 1.33 Vein of Galen aneurysm in a 3-day-old female baby, accompanied by an aneurysm of the internal cerebral veins (from Akira Hori's archives)

the result of accelerated growth of the ganglionic eminences. Subsequent venous changes depend largely upon the expansion of the cerebral and cerebellar hemispheres and the relatively late ossification of the skull (Fig. 1.32 e, f). One of the most common malformations of the cerebral venous system is the **vein of Galen malformation** (Fig. 1.33).

1.11 Development of Fibre Tracts (Including Development of Myelination)

Early generated, 'pioneer' neurons lay down an axonal scaffold, containing guidance cues that are available to later outgrowing axons (Chap. 2). The first descending brain stem projections to the spinal cord can be viewed as pioneer fibres. They arise in the interstitial nucleus of the fasciculus longitudinalis medialis (flm) and in the reticular formation (Müller and O'Rahilly 1988 a, b). At early developmental stages (from stage 11/12 onwards), in the brain stem a ventral longitudinal tract can be distinguished, followed by lateral and medial longitudinal fasciculi at stage 13. Descending fibres from the medullary

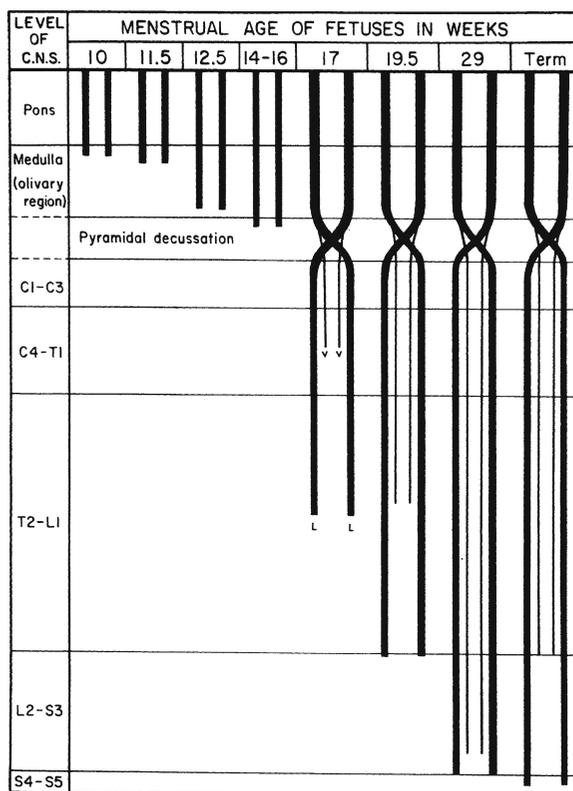


Fig. 1.34 The outgrowth of the human corticospinal tracts (after Humphrey 1960)

reticular formation reach the spinal cord in embryos of 10–12-mm CRL (Windle and Fitzgerald 1937). Interstitiospinal fibres from the interstitial nucleus of the flm start to descend at stage 13, i.e. at 28 days. In 12-mm-CRL embryos (about stage 17/18), vestibulospinal projections were found (Windle 1970). At the end of the embryonic period, the flm is well developed, and receives ascending and descending (the medial vestibulospinal tract) components from the vestibular nuclear complex (Müller and O'Rahilly 1990c). The lateral vestibulospinal tract arises from the lateral vestibular nucleus. Windle and Fitzgerald (1937) also followed the ingrowth of dorsal root projections and the development of commissural, ascending and descending spinal pathways (Chap. 6). Ascending fibres in the dorsal funiculus have reached the brain stem at stage 16 (Müller and O'Rahilly 1989). Decussating fibres, forming the medial lemniscus, were first noted at stage 20 (Müller and O'Rahilly 1990a, b; Chap. 7).

The **corticospinal tract** is one of the latest developing descending pathways (ten Donkelaar 2000). At stage 21, the cortical plate starts to develop, whereas a definite internal capsule is present by stage 22 (Müller and O'Rahilly 1990b). Hewitt (1961) found

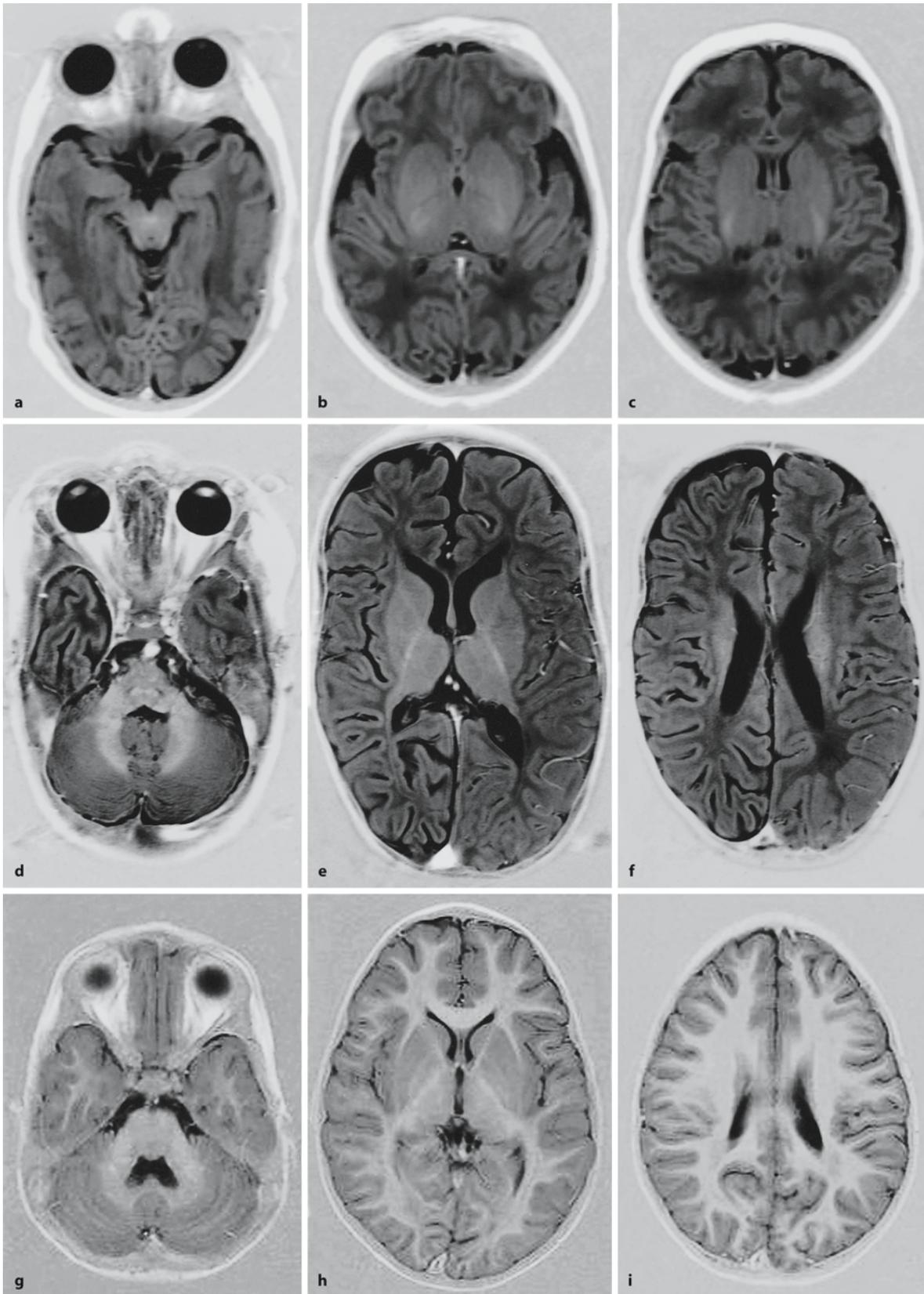


Fig. 1.36 Myelination in T1-weighted horizontal (or axial) images of a newborn (**a–c**), a child of 1.5 years of age (**d–f**) and a young adult (**g–i**). In **a** myelination is visible in the decussation

of the brachia conjunctiva, and in **b** and **c** in the posterior limb of the internal capsule. Myelination is far more advanced in the pictures of the infant (**d–f**)

in the lateral part of the posterior limb of the internal capsule and the central part of the corona radiata; therefore, at birth the human brain is rather immature in regard to the extent of its myelination. The rate of deposition of myelin is greatest during the first two postnatal years (van der Knaap and Valk 1990, 1995). On magnetic resonance images, a significant decrease in water content leads to a decrease in longitudinal relaxation times (T1) and transverse relaxation times (T2). Consequently, 'adult-like' appearance of T1-weighted and T2-weighted images becomes evident towards the end of the first year of life. Age-related changes in white matter myelination continue during childhood and adolescence (Paus et al. 2001). The pattern of myelination around birth is illustrated in Fig. 1.36.

Prenatal motor behaviour has been analysed in ultrasound studies. The first, just discernable movements emerge at 6–7 weeks' postmenstrual age (Ianiruberto and Tajani 1981; de Vries et al. 1982). About 2 weeks later, movements involving all parts of the body appear. Two major forms of such movements can be distinguished, the startle and the general movement (Hadders-Algra and Forssberg 2002). The first movements appear prior to the formation of the spinal reflex arc, which is completed at 8 weeks' postmenstrual age (Okado and Kojima 1984). This means that the first human movements, just like those of chick embryos (Hamburger et al. 1966), are generated in the absence of afferent information. During the following weeks, new movements are added to the fetal repertoire, such as isolated arm and leg movements, various movements of the head, stretches, periodic breathing movements and sucking and swallowing movements (de Vries et al. 1982). Arm and leg movements, just like the palmar and plantar grasp reflexes, develop at 9–12 weeks, suggesting that fetal motility develops without a clear craniocaudal sequence. The age at which the various movements develop shows considerable interindividual variation, but at about 16 weeks' postmenstrual age all fetuses exhibit the entire fetal repertoire. The repertoire continues to be present throughout gestation (Hadders-Algra and Forssberg 2002). If these movements are diminished or even absent owing to cerebral, spinal, nervous or muscular defects, the *fetal akinesia deformation sequence* occurs (Moessinger 1983), the phenotype of which was first described as Pena–Shokeir phenotype. This phenotype is characterized by multiple joint contractures, limb pterygia, lung hypoplasia, short umbilical cord, craniofacial deformities, growth retardation, hydrops and polyhydramnion (Hall 1986). The fetal akinesia sequence has been detected by ultrasound as early as 13 weeks of gestation owing to cerebral deformities leading to hydranencephaly (Witters et al. 2002) and at 16 weeks of gestation in a case of muscular origin (Lammens et al. 1997).

References

- Acampora D, Gulisano M, Broccoli V, Simeone A (2001) Otx genes in brain morphogenesis. *Prog Neurobiol* 64:69–95
- Aicardi J (1992) Diseases of the Nervous System in Childhood. Clinics in Developmental Medicine. Nr 115/118. Mac Keith, London
- Aida N, Nishimura G, Hachiya Y, Matsui K, Takeuchi M, Itani Y (1998) MR imaging of perinatal brain damage: Comparison of clinical outcome with initial and follow-up MR findings. *AJNR Am J Neuroradiol* 19:1909–1921
- Allsop G, Gamble HJ (1979) Light and electron microscopic observations on the development of the blood vascular system of the human brain. *J Anat (Lond)* 128:461–477
- Altman J, Bayer SA (1997) Development of the Cerebellar System: In relation to its evolution, structure and functions. CRC, Boca Raton, FL
- Anderson SA, Mione M, Yun K, Rubinstein JLR (1999) Differential origins of neocortical projection and local circuit neurons: Role of Dlx genes in neocortical interneuronogenesis. *Cereb Cortex* 9:646–654
- Anderson SA, Marín O, Horn C, Jennings K, Rubinstein JLR (2001) Distinct cortical migrations from the medial and lateral ganglionic eminences. *Development* 128:353–363
- Ariëns Kappers JA (1958) Structural and functional changes in the telencephalic choroid plexus during brain ontogenesis. In: Wolstenholme GEW, O'Connor CM (eds) *The Cerebrospinal Fluid*. Little, Brown, Boston, MA, pp 3–25
- Arnold SE, Trojanowski JQ (1996) Human fetal hippocampal development: I. Cytoarchitecture, myeloarchitecture, and neuronal morphologic features. *J Comp Neurol* 367:274–292
- Banker BQ, Larroche JC (1962) Periventricular leukomalacia of infancy. *Arch Neurol* 7:386–410
- Barkovich AJ (2000) *Pediatric Neuroimaging*, 3rd ed. Lippincott, Philadelphia, PA
- Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB (2001) Classification system for malformations of cortical development. Update 2001. *Neurology* 57:2168–2178
- Bartelmez GW (1923) The subdivisions of the neural folds in man. *J Comp Neurol* 35:231–295
- Bartelmez GW, Dekaban AS (1962) The early development of the human brain. *Contrib Embryol Carnegie Instn* 37:13–32
- Barth PG (1993) Pontocerebellar hypoplasias. An overview of a group of inherited neurodegenerative disorders with fetal onset. *Brain Dev* 15:411–422
- Bayer SA, Altman J (1991) *Neocortical Development*. Raven, New York
- Bayer SA, Altman J (2002) *The Spinal Cord from Gestational Week 4 to the 4th Postnatal Month*. CRC, Boca Raton, FL
- Bayer SA, Altman J, Russo RJ, Zhang X (1995) Embryology. In: Duckett S (ed) *Pediatric Neuropathology*. Williams & Wilkins, Baltimore, MD, pp 54–107
- Ben-Arie N, Bellen HJ, Armstrong DL, McCall AE, Gordadze PR, Guo Q, Matzuk MM, Zoghbi HY (1997) *Math1* is essential for genesis of cerebellar granule neurons. *Nature* 390:169–172
- Bergquist H (1952) The formation of neuromeres in Homo. *Acta Soc Med Ups* 57:23–32
- Blaas H-GK (1999) *The Embryonic Examination. Ultrasound studies on the development of the human embryo*. Thesis, Norwegian University of Science and Technology, Trondheim. TAPIR, Trondheim, Norway
- Blaas H-GK, Eik-Nes SH (1996) Ultrasound assessment of early brain development. In: Jurkovic D, Jauniaux E (eds) *Ultrasound and Early Pregnancy*. Parthenon, New York, pp 3–18

- Blaas H-G, Eik-Nes SH (2002) The description of the early development of the human central nervous system using two-dimensional and three-dimensional ultrasound. In: Lagercrantz H, Hanson M, Evrard P, Rodeck CH (eds) *The Newborn Brain—Neuroscience and clinical applications*. Cambridge University Press, Cambridge, pp 278–288
- Blaas H-G, Eik-Nes SH, Kiserud T, Hellevik LR (1994) Early development of the forebrain and midbrain: A longitudinal ultrasound study from 7 to 12 weeks of gestation. *Ultrasound Obstet Gynecol* 4:183–192
- Blaas H-G, Eik-Nes SH, Kiserud T, Berg S, Angelsen B, Olstad B (1995a) Three-dimensional imaging of the brain cavities in human embryos. *Ultrasound Obstet Gynecol* 5:228–232
- Blaas H-G, Eik-Nes SH, Kiserud T, Hellevik LR (1995b) Early development of the hindbrain: A longitudinal ultrasound study from 7 to 12 weeks of gestation. *Ultrasound Obstet Gynecol* 5:151–160
- Brazel CY, Romanko MJ, Rothstein RP, Levison SW (2003) Roles of the mammalian subventricular zone in brain development. *Prog Neurobiol* 69:49–69
- Brody BA, Kinney HC, Kloman AS, Gilles FH (1987) Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. *J Neuropathol Exp Neurol* 46:283–301
- Brun A (1965) The subpial granular layer of the foetal cerebral cortex in man. Its ontogeny and significance in congenital cortical malformations. *Acta Pathol Microbiol Scand* 179(Suppl):1–98
- Bulfone A, Puelles L, Porteus MH, Frohman MA, Martin GR, Rubinstein JLR (1993) Spatially restricted expression of *Dlx-1*, *Dlx-2*, (*Tes-1*), *Gbx-2*, and *Wnt-3* in the embryonic day 12.5 mouse forebrain defines potential transverse and longitudinal boundaries. *J Neurosci* 13:3155–3172
- Carlson BM (1999) *Human Embryology & Development*, 2nd ed. Mosby, St. Louis, MO
- Collins P, Billett FS (1995) The terminology of early development. *Clin Anat* 8:418–425
- Congdon ED (1922) Transformation of the aortic-arch system during the development of the human embryo. *Contrib Embryol Carnegie Instn* 14:47–110
- Corner GW (1929) A well-preserved human embryo of 10 somites. *Contrib Embryol Carnegie Instn* 20:81–102
- Crelin EA (1973) *Functional Anatomy of the Newborn*. Yale University Press, London
- de Carlos JA, Lopez-Mascaraque L, Valverde F (1996) Dynamics of cell migration from the lateral ganglionic eminence in the rat. *J Neurosci* 16:6146–6156
- de Souza FSJ, Niehrs C (2000) Anterior endoderm and head induction in early vertebrate embryos. *Cell Tissue Res* 300:207–217
- De Reuck J, Chattha AS, Richardson EPJ (1972) Pathogenesis and evolution of periventricular leukomalacia in infancy. *Arch Neurol* 27:229–236
- de Vries JIP, Visser GHA, Prechtl HFR (1982) The emergence of fetal behaviour. I. Qualitative aspects. *Early Hum Dev* 7:301–322
- Doetsch F, García-Verdugo JM, Alvarez-Buylla A (1997) Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain. *J Neurosci* 17:5046–5061
- Duckett S (1971) The establishment of internal vascularization in the human telencephalon. *Acta Anat (Basel)* 80:107–113
- Duvernoy HM (1998) *The Human Hippocampus. Functional anatomy, vascularization and serial sections with MRI*, 2nd ed. Springer, Berlin Heidelberg New York
- Essick CR (1912) The development of the nuclei pontis and the nucleus arcuatus in man. *Am J Anat* 13:25–54
- Evans HM (1911) Die Entwicklung des Blutgefäßsystems. In: Keibel F, Mall FP (Hrsg) *Handbuch der Entwicklungsgeschichte des Menschen, Zweiter Band. Hirzel, Leipzig*, pp 551–688
- Evans HM (1912) The development of the vascular system. In: Keibel F, Mall FP (eds) *Manual of Human Embryology, Vol 2*. Lippincott, Philadelphia, PA, pp 570–709
- Favier B, Dollé P (1997) Developmental functions of mammalian *Hox* genes. *Mol Hum Reprod* 3:115–131
- Feess-Higgins A, Larroche J-C (1987) Le développement du cerveau foetal humain. *Atlas anatomique*. Masson, Paris
- Flechsig PE (1920) *Anatomie des menschlichen Gehirns und Rückenmarks auf myelogenetischer Grundlage*. Thieme, Leipzig
- Gadisseux J-F, Goffinet AM, Lyon G, Evrard P (1992) The human transient subpial granular layer: An optical, immunohistochemical, and ultrastructural analysis. *J Comp Neurol* 324:94–114
- Garel C (2004) *MRI of the Fetal Brain. Normal development and cerebral pathologies*. Springer, Berlin Heidelberg New York
- Gardner RJM, Coleman LT, Mitchell LA, Smith LJ, Harvey AS, Schefker IE, Storey E, Nowotny MJ, Sloane RA, Lubitz L (2001) Near-total absence of the cerebellum. *Neuropediatrics* 32:62–68
- Gilles FH, Shankle W, Dooling EC (1983) Myelinated tracts. In: Gilles FH, Leviton A, Dooling EC (eds) *The Developing Human Brain*. Wright, Bristol, pp 117–183
- Gillilan LA (1972) Anatomy and embryology of the arterial system of the brain stem and cerebellum. *Handb Clin Neurol* 11:24–44
- Gleeson JG, Walsh CA (2000) Neuronal migration disorders: From genetic diseases to developmental mechanisms. *Trends Neurosci* 23:352–359
- Golden JA (1998) Holoprosencephaly: A defect in brain patterning. *J Neuropathol Exp Neurol* 57:991–999
- Gribnau AAM, Geijsberts LGM (1985) Morphogenesis of the brain in staged rhesus monkey embryos. *Adv Anat Embryol Cell Biol* 91:1–69
- Hadders-Algra M, Forssberg H (2002) Development of motor functions in health and disease. In: Lagercrantz H, Hanson M, Evrard P, Rodeck CH (eds) *The Newborn Brain—Neuroscience and clinical applications*. Cambridge University Press, Cambridge, pp 479–507
- Hall JG (1986) Analysis of Pena Shokeir phenotype. *Am J Med Genet* 25:99–117
- Hambleton G, Wigglesworth JS (1976) Origin of intraventricular haemorrhage in the preterm infant. *Arch Child Dis* 51:651–659
- Hamburger V, Wenger E, Oppenheim RW (1966) Motility in the chick embryo in the absence of sensory input. *J Exp Zool* 162:133–160
- Hamilton WJ, Mossman HW (1972) *Hamilton, Boyd and Mossman's Human Embryology. Prenatal development of form and function*, 4th ed. Heffer, Cambridge
- Hatten ME (1999) Central nervous system neuronal migration. *Annu Rev Neurosci* 22:511–539
- Hatten ME, Alder J, Zimmerman K, Heintz N (1997) Genes involved in cerebellar cell specification and differentiation. *Curr Opin Neurobiol* 7:40–47
- Heuser CH, Corner GW (1957) Developmental horizons in human embryos. Description of age group X, 4 to 12 somites. *Contrib Embryol Carnegie Instn* 36:29–39
- Hevner RF, Kinney HC (1996) Reciprocal entorhinal-hippocampal connections established by human fetal midgestation. *J Comp Neurol* 372:384–394
- Hewitt W (1961) The development of the human internal capsule and lentiform nucleus. *J Anat (Lond)* 95:191–199
- His W (1880) *Anatomie menschlicher Embryonen. I. Embryonen des ersten Monats*. Vogel, Leipzig

- His W (1889) Die Formentwicklung des menschlichen Vorderhirns vom Ende des ersten bis zum Beginn des dritten Monats. *Abh Kön Sächs Ges Wiss, Math Phys Kl* 15:675–735
- His W (1890) Die Entwicklung des menschlichen Rautenhirns vom Ende des ersten bis zum Beginn des dritten Monats. I. Verlängertes Mark. *Abh Kön Sächs Ges Wiss, Math Phys Kl* 29:1–74
- His W (1904) Die Entwicklung des menschlichen Gehirns während der ersten Monate. Hirzel, Leipzig
- Hochstetter F (1919) Beiträge zur Entwicklungsgeschichte des menschlichen Gehirns, I. Teil. Deuticke, Vienna
- Hochstetter F (1929) Beiträge zur Entwicklungsgeschichte des menschlichen Gehirns, II. Teil, 3. Lieferung. Die Entwicklung des Mittel- und Rautenhirns. Deuticke, Vienna
- Hochstetter F (1934) Über die Entwicklung und Differenzierung der Hüllen des Rückenmarkes beim Menschen. *Morphol Jahrb* 74:1–104
- Hochstetter F (1939) Über die Entwicklung und Differenzierung der Hüllen des menschlichen Gehirns. *Morphol Jahrb* 83:359–494
- Hori A, Friede RL, Fischer G (1983) Ventricular diverticles with localized dysgenesis of the temporal lobe in a cloverleaf skull anomaly. *Acta Neuropathol (Berl)* 60:132–136
- Hori A, Eubel R, Ulbrich R (1984a) Congenital ventricular diverticulum in the brainstem. Report of four cases. *Acta Neuropathol (Berl)* 63:330–333
- Hori A, Bardosi A, Tsuboi K, Maki Y (1984b) Accessory cerebral ventricle of the occipital lobe. Morphogenesis and clinical and pathological appearance. *J Neurosurg* 61:767–771
- Humphrey T (1960) The development of the pyramidal tracts in human fetuses, correlated with cortical differentiation. In: Tower DB, Schadé JP (eds) *Structure and Function of the Cerebral Cortex*. Elsevier, Amsterdam, pp 93–103
- Humphrey T (1966) The development of the human hippocampal formation correlated with some aspects of its phylogenetic history. In: Hassler R, Stephan H (eds) *Evolution of the Forebrain*. Thieme, Stuttgart, pp 104–116
- Ianniruberto A, Tajani E (1981) Ultrasonographic study of fetal movements. *Sem Perinatol* 5:175–181
- Inoue T, Nakamura S, Osumi N (2000) Fate mapping of the mouse prosencephalic neural plate. *Dev Biol* 219:373–383
- Jakob A (1928) Das Kleinhirn. In: von Möllendorf W (ed) *Handbuch der mikroskopischen Anatomie des Menschen, Vol 4, Teil 1*. Springer, Berlin Heidelberg New York, pp 674–916
- Jeffery N (2002) Differential regional brain growth and rotation of the prenatal human tentorium cerebelli. *J Anat (Lond)* 200:135–144
- Jirásek JE (1983) *Atlas of Human Prenatal Morphogenesis*. Nijhoff, Baltimore, MD
- Jirásek JE (2001) *An Atlas of the Human Embryo and Fetus*. Parthenon, New York
- Jirásek JE (2004) *An Atlas of Human Prenatal Developmental Mechanisms. Anatomy and staging*. Taylor & Francis, London, New York
- Kahle W (1969) Die Entwicklung der menschlichen Grosshirnhemisphäre. *Schriften Neurol* 1:1–116
- Keibel F, Elze C (1908) *Normentafeln zur Entwicklungsgeschichte des Menschen*. Hirzel, Leipzig
- Keyser AJM (1972) The development of the diencephalon of the Chinese hamster. *Acta Anat (Basel)* 83(Suppl 59):1–178
- Kinney HC, Brody BA, Kroman AS, Gilles FH (1988) Sequence of central nervous system myelination in human infancy. II. Patterns of myelination in autopsied infants. *J Neuropathol Exp Neurol* 47:217–234
- Klintworth GK (1967) The ontogeny and growth of the human tentorium cerebelli. *Anat Rec* 158:433–442
- Kollias SS, Ball WS (1997) Congenital malformations of the brain. In: Ball WS (ed) *Pediatric Neuroradiology*. Lippincott, Philadelphia, PA, pp 91–174
- Konstantinidou AD, Silos-Santiago I, Flaris N, Snider WD (1995) Development of the primary afferent projection in human spinal cord. *J Comp Neurol* 354:1–12
- Kornack DR, Rakic P (2001) The generation, migration, and differentiation of olfactory neurons in the adult primate brain. *Proc Natl Acad Sci USA* 98:4752–4757
- Kraus I, Jirásek JE (2002) Some observations of the structure of the choroid plexus and its cysts. *Prenat Diagn* 22:1223–1228
- Kuban KCK, Gilles FH (1985) Human telencephalic angiogenesis. *Ann Neurol* 17:539–548
- Lammens M, Moerman P, Fryns JP, Lemmens F, van de Kamp GM, Goemans N, Dom R (1997) Fetal akinesia sequence caused by nemaline myopathy. *Neuropediatrics* 28:116–119
- Langman J (1963) *Medical Embryology*. Williams & Wilkins, Baltimore, MD
- Lavdas AA, Grigoriou M, Pachnis V, Parnavelas JG (1999) The medial ganglionic eminence gives rise to a population of early neurons in the developing cerebral cortex. *J Neurosci* 19:7881–7888
- Le Douarin NM, Kalcheim C (1999) *The Neural Crest*, 2nd ed. Cambridge University Press, Cambridge
- Lemire RJ, Loeser JD, Leech RW, Alvord EC (1975) *Normal and Abnormal Development of the Human Nervous System*. Harper & Row, Hagerstown, MD
- Letinić K, Kostović I (1997) Transient fetal structure, the gangliothalamic body, connects telencephalic germinal zone with all thalamic regions in the developing human brain. *J Comp Neurol* 384:373–395
- Letinić K, Rakic P (2001) Telencephalic origin of human thalamic GABAergic neurons. *Nat Neurosci* 9:931–936
- Lie KTA (1968) *Congenital Anomalies of the Carotid Arteries*. Thesis, University of Amsterdam. Excerpta Medica Foundation, Amsterdam
- Lindenberg R (1956) Die Gefäßversorgung und ihre Bedeutung für Art und Ort von kreislaufgedingten Gewebsschäden und Gefäßprozessen. In: Lubarsch-Henke-Rössle's *Handbuch der speziellen pathologischen Anatomie und Histologie, Vol 13 (Scholz W, Hrsg), Teil 1B*. Springer, Berlin Heidelberg New York, pp 1071–1164
- Luckett WP (1978) Origin and differentiation of the yolk sac and extraembryonic mesoderm in presomite human and rhesus monkey embryos. *Am J Anat* 152:59–97
- Lumsden A, Krumlauf AR (1996) Patterning the vertebrate neuraxis. *Science* 274:1109–1115
- Macchi G (1951) The ontogenetic development of the olfactory telencephalon in man. *J Comp Neurol* 95:245–305
- Marín O, Rubinstein JLR (2001) A long, remarkable journey: Tangential migration in the telencephalon. *Nat Rev Neurosci* 2:780–790
- Marín O, Rubinstein JLR (2002) Patterning, regionalization, and cell differentiation in the forebrain. In: Rossant J, Tam PPL (eds) *Mouse Development—Patterning, Morphogenesis, and Organogenesis*. Academic, San Diego CA, pp 75–106
- Marín O, Anderson SA, Rubinstein JLR (2000) Origin and molecular specification of striatal interneurons. *J Neurosci* 20:6063–6076
- Marín O, Yaron A, Bagri A, Tessier-Lavigne M, Rubinstein JLR (2001) Sorting of striatal and cortical interneurons regulated by semaphorin-neuropilin interactions. *Science* 293:872–875
- Marín-Padilla M (1990) Origin, formation, and prenatal maturation of the human cerebral cortex: An overview. *J Craniofac Genet Dev Biol* 10:137–146

- Marín-Padilla M (1996) Developmental neuropathology and impact of perinatal brain damage. I. Hemorrhagic lesions of neocortex. *J Neuropathol Exp Neurol* 55:758–773
- Marín-Padilla M (1997) Developmental neuropathology and impact of perinatal brain damage. II. White matter lesions of the neocortex. *J Neuropathol Exp Neurol* 56:219–235
- Marín-Padilla M (1998) Cajal-Retzius cells and the development of the neocortex. *Trends Neurosci* 21:64–71
- Marín-Padilla M (1999) Developmental neuropathology and impact of perinatal brain damage. III. Gray matter lesions of the neocortex. *J Neuropathol Exp Neurol* 58: 407–429
- Marti E, Bovolenta P (2002) Sonic hedgehog in CNS development: One signal, multiple outputs. *Trends Neurosci* 25:89–96
- Mehler MF, Mabie PC, Zhang D, Kessler JA (1997) Bone morphogenetic proteins in the nervous system. *Trends Neurosci* 20:309–317
- Meyer G, Goffinet AM (1998) Prenatal development of reelin-immunoreactive neurons in the human neocortex. *J Comp Neurol* 397:29–40
- Meyer G, Wahle P (1999) The paleocortical ventricle is the origin of reelin-expressing neurons in the marginal zone of the foetal human neocortex. *Eur J Neurosci* 11:3937–3944
- Meyer G, Goffinet AM, Fairén A (1999) What is a Cajal-Retzius cell? A reassessment of a classical cell type based on recent observations in the developing neocortex. *Cereb Cortex* 9:765–775
- Meyer G, Schaaps JP, Moreau L, Goffinet AM (2000) Embryonic and early fetal development of the human neocortex. *J Neurosci* 20:1858–1868
- Millen KJ, Millonig JH, Wingate RJT, Alder J, Hatten ME (1999) Neurogenetics of the cerebellar system. *J Child Neurol* 14:574–582
- Moessinger AC (1983) Fetal akinesia deformation sequence: An animal model. *Pediatrics* 72:857–863
- Monuki ES, Walsh CA (2001) Mechanisms of cerebral cortical patterning in mice and human. *Nat Neurosci* 4:1199–1206
- Moore KL, Persaud TVN, Shiota K (2000) *Color Atlas of Clinical Embryology*, 2nd ed. Saunders, Philadelphia, PA
- Muenke M, Beachy PA (2000) Genetics of ventral forebrain development and holoprosencephaly. *Curr Opin Genet Dev* 10:262–269
- Müller F, O’Rahilly R (1983) The first appearance of the major divisions of the human brain at stage 9. *Anat Embryol (Berl)* 168:419–432
- Müller F, O’Rahilly R (1985) The first appearance of the neural tube and optic primordium in the human embryo at stage 10. *Anat Embryol (Berl)* 172:157–169
- Müller F, O’Rahilly R (1988a) The development of the human brain from a closed neural tube at stage 13. *Anat Embryol (Berl)* 177:203–224
- Müller F, O’Rahilly R (1988b) The first appearance of the future cerebral hemispheres in the human embryo at stage 14. *Anat Embryol (Berl)* 177:495–511
- Müller F, O’Rahilly R (1989) The human brain at stage 16, including the initial evagination of the neurohypophysis. *Anat Embryol (Berl)* 179:551–569
- Müller F, O’Rahilly R (1990a) The human brain at stages 18–20, including the choroid plexuses and the amygdaloid and septal nuclei. *Anat Embryol (Berl)* 182:285–306
- Müller F, O’Rahilly R (1990b) The human brain at stages 21–23, with particular reference to the cerebral cortical plate and to the development of the cerebellum. *Anat Embryol (Berl)* 182:375–400
- Müller F, O’Rahilly R (1990c) The human rhombencephalon at the end of the embryonic period proper. *Am J Anat* 189:127–145
- Müller F, O’Rahilly R (1997) The timing and sequence of appearance of neuromeres and their derivatives in staged human embryos. *Acta Anat (Basel)* 158:83–99
- Nakamura M, Roser F, Rundschuh O, Vorkapic P, Samii M (2003) Intraventricular meningiomas: A review of 16 cases with reference to the literature. *Surg Neurol* 59:491–503
- Nakatsu T, Uwabe C, Shiota K (2000) Neural tube closure in humans initiates at multiple sites: Evidence from human embryos and implications for the pathogenesis of neural tube defects. *Anat Embryol (Berl)* 201:455–466
- Nelson MD, Gonzalez-Gomez I, Gilles FH (1991) The search for human telencephalic ventriculofugal arteries. *Am J Neuroradiol* 12:215–222
- Niemann G, Wakat JP, Krägeloh-Mann I, Grodd W, Michaelis R (1994) Congenital hemiparesis and periventricular leukomalacia: Pathogenetic aspects on magnetic resonance imaging. *Dev Med Child Neurol* 36:943–950
- Nieuwenhuys R (1998) Morphogenesis and general structure. In: Nieuwenhuys R, ten Donkelaar HJ, Nicholson C *The Central Nervous System of Vertebrates*. Springer, Berlin Heidelberg New York, pp 159–228
- Nieuwkoop PD, Albers B (1990) The role of competence in the craniocaudal segregation of the central nervous system. *Dev Growth Diff* 32:23–31
- Nishimura H, Semba R, Tanimura T, Tanaka O (1977) *Prenatal Development of the Human with Special Reference to Craniofacial Structures*. An atlas. Department of Health, Education & Welfare, National Institute of Health, Bethesda, MD
- Noden DM (1991) Cell movements and control of patterned tissue assembly during craniofacial development. *J Craniofac Genet Dev Biol* 11:192–213
- Norman MG, O’Kusky JR (1986) The growth and development of microvasculature in human cerebral cortex. *J Neuropathol Exp Neurol* 45:222–232
- Norman MG, McGillivray BC, Kalousek DK, Hill A, Poskitt KJ (1995) *Congenital Malformations of the Brain*. Pathological, embryological, clinical, radiological and genetic aspects. Oxford University Press, New York
- Okado N (1981) Onset of synapse formation in the human spinal cord. *J Comp Neurol* 201:211–219
- Okado N, Kojima T (1984) Ontogeny of the central nervous system: Neurogenesis, fibre connections, synaptogenesis and myelination in the spinal cord. In: Prectl HFR (ed) *Continuity of Neural Functions from Prenatal to Postnatal Life*. Blackwell, Oxford, pp 31–45
- Okado N, Kahimi S, Kojima T (1979) Synaptogenesis in the cervical cord of the human embryo: Sequence of synapse formation in a spinal reflex pathway. *J Comp Neurol* 184:491–517
- Okudera T, Ohta T, Huang YP, Yokota A (1988) Development and radiological anatomy of the superficial cerebral convexity vessels in the human fetus. *J Neuroradiol* 15:205–224
- Olson EC, Walsh CA (2002) Smooth, rough and upside-down neocortical development. *Curr Opin Genet Dev* 12:320–327
- Opitz JM (1993) Blastogenesis and the “primary field” in human development. *Birth Defects* 29:3–37
- Opitz JM, Wilson GN, Gilbert-Barnes E (1997) Abnormalities of blastogenesis, organogenesis, and phenogenesis. In: Gilbert-Barnes E (ed) *Potter’s Pathology of the Fetus and Infant*. Mosby, St. Louis, pp 65–105
- O’Rahilly R (1973) *Developmental Stages in Human Embryos*. Part A: Embryos of the first three weeks (stages 1 to 9). Carnegie Institution of Washington Publication 631, Washington, DC

- O'Rahilly R (1975) A Color Atlas of Human Embryology. A slide presentation. Saunders, Philadelphia, PA
- O'Rahilly R, Gardner E (1979) The initial development of the human brain. *Acta Anat (Basel)* 104:123–133
- O'Rahilly R, Müller F (1981) The first appearance of the human nervous system at stage 8. *Anat Embryol (Berl)* 163:1–13
- O'Rahilly R, Müller F (1986) The meninges in human development. *J Neuropathol Exp Neurol* 45:588–608
- O'Rahilly R, Müller F (1987) Developmental Stages in Human Embryos. Carnegie Institution of Washington Publication 637, Washington, DC
- O'Rahilly R, Müller F (1999) The Embryonic Human Brain. An atlas of developmental stages, 2nd ed. Wiley-Liss, New York
- O'Rahilly R, Müller F (2001) Human Embryology & Teratology, 3rd ed. Wiley-Liss, New York
- Padgett DH (1948) The development of the cranial arteries in the human embryo. *Contrib Embryol Carnegie Instn* 32:205–261
- Padgett DH (1957) The development of the cranial venous system in man, from the viewpoint of comparative anatomy. *Contrib Embryol Carnegie Instn* 36:79–140
- Parnavelas JG (2000) The origin and migration of cortical neurons: New vistas. *Trends Neurosci* 23:126–131
- Paus T, Collins DL, Evans AC, Leonard G, Pike B, Zijdenbos A (2001) Maturation of white matter in the human brain: A review of magnetic resonance studies. *Brain Res Bull* 54:255–266
- Pearce WJ (2002) Cerebrovascular regulation in the neonate. In: Lagercrantz H, Hanson M, Evrard P, Rodeck CH (eds) *The Newborn Brain—Neuroscience and clinical applications*. Cambridge University Press, Cambridge, pp 252–277
- Pearlman AL, Faust PL, Hatten ME, Brunstrom JE (1998) New directions for neuronal migration. *Curr Opin Neurobiol* 8:45–54
- Pearson AA (1941) The development of the olfactory nerve in man. *J Comp Neurol* 75:199–217
- Pilz D, Stoodley N, Golden JA (2002) Neuronal migration, cerebral cortical development, and cerebral cortical anomalies. *J Neuropathol Exp Neurol* 61:1–11
- Pooh RK, Maeda K, Pooh K (2003) An Atlas of Fetal Central Nervous System Diseases. Diagnosis and treatment. Parthenon, Boca Raton, FL
- Puelles L, Rubinstein JLR (1993) Expression patterns of homeobox and other putative regulatory genes in the embryonic forebrain suggest a neuromeric organization. *Trends Neurosci* 16:472–479
- Puelles L, Rubinstein JLR (2003) Forebrain gene expression domains and the evolving prosomeric model. *Trends Neurosci* 26:469–476
- Puelles L, Verney C (1998) Early neuromeric distribution of tyrosine-hydroxylase-immunoreactive neurons in human embryos. *J Comp Neurol* 394:283–308
- Puelles L, Kuwana E, Puelles E, Bulfone A, Shimamura K, Keleher J, Smiga S, Rubinstein JLR (2000) Pallial and subpallial derivatives in the embryonic chick and mouse telencephalon, traced by the expression of the genes *Dlx-2*, *Emx-1*, *Nkx-2.1*, *Pax-6*, and *Tbr-1*. *J Comp Neurol* 424:409–438
- Rakic P (1972) Mode of cell migration to the superficial layers of fetal monkey neocortex. *J Comp Neurol* 145:61–84
- Rakić P, Sidman RL (1969) Telencephalic origin of pulvinar neurons in the fetal human brain. *Z Anat Entw Gesch* 129:53–82
- Rakic P, Sidman RL (1970) Histogenesis of cortical layers in human cerebellum, particularly the lamina dissecans. *J Comp Neurol* 139:473–500
- Rakic P, Yakovlev PI (1968) Development of the corpus callosum and cavum septi in man. *J Comp Neurol* 132:45–72
- Ramaekers VT, Heimann G, Reul J, Thron A, Jaeken J (1997) Genetic disorders and cerebellar structural abnormalities in childhood. *Brain* 120:1739–1751
- Ranke G (1910) Beiträge zur Kenntnis der normalen und pathologischen Hirnrindenbildung. *Ziegl Beitr Path Anat* 47:51–125
- Rhinn M, Brand M (2001) The midbrain-hindbrain boundary organizer. *Curr Opin Neurobiol* 11:34–42
- Rijli FM, Gavalas A, Chambon P (1998) Segmentation and specification in the branchial region of the head: The role of the *Hox* selector genes. *Int J Dev Biol* 42:393–401
- Rorke LB (1992) Anatomical features of the developing brain implicated in pathogenesis of hypoxic-ischemic injury. *Brain Pathol* 2:211–221
- Rubinstein JLR, Beachy PA (1998) Patterning of the embryonic forebrain. *Curr Opin Neurobiol* 8:18–26
- Rubinstein JLR, Shimamura K, Martinez S, Puelles L (1998) Regionalization of the prosencephalic neural plate. *Annu Rev Neurosci* 21:445–477
- Ruggieri PM (1997) Metabolic and neurodegenerative disorders and disorders with abnormal myelination. In: Ball WS (ed) *Pediatric Neuroradiology*. Lippincott, Philadelphia, PA, pp 175–237
- Salas E, Ziyal IM, Sekhar LN, Wright DC (1998) Persistent trigeminal artery: An anatomic study. *Neurosurgery* 43:557–562
- Sarnat HB (2000) Molecular genetic classification of central nervous system malformations. *J Child Neurol* 15:675–687
- Sarnat HB, Flores-Sarnat L (2001) Neuropathologic research strategies in holoprosencephaly. *J Child Neurol* 16:918–931
- Schuermans C, Guillemot F (2002) Molecular mechanisms underlying cell fate specification in the developing telencephalon. *Curr Opin Neurobiol* 12:26–34
- Sensenig EC (1951) The early development of the meninges of the spinal cord in human embryos. *Contrib Embryol Carnegie Instn* 34:145–157
- Seress L, Ábrahám H, Tornóczy T, Kosztolányi G (2001) Cell formation in the human hippocampal formation from mid-gestation to the late postnatal period. *Neuroscience* 105:831–843
- Shimamura K, Hartigan DJ, Martinez S, Puelles L, Rubinstein JLR (1995) Longitudinal organization of the anterior neural plate and neural tube. *Development* 121:3923–3933
- Sidman RL, Rakic P (1982) Development of the human central nervous system. In: Haymaker W, Adams RD (eds) *Histology and Histopathology of the Nervous System*. Thomas, Springfield, IL, pp 3–145
- Sie LTL, van der Knaap MS, van Wezel-Meijler G, Valk J (1997) MRI assessment of myelination of motor and sensory pathways in the brain of preterm and term-born infants. *Neuropediatrics* 28:97–105
- Spreatico R, Arcelli P, Frassoni C, Canetti P, Giaccone G, Rizzutti T, Mastrangelo M, Bentivoglio M (1999) Development of layer I of the human cerebral cortex after midgestation: Architectonic findings, immunocytochemical identification of neurons and glia, and in situ labeling of apoptotic cells. *J Comp Neurol* 410:126–142
- Squier W (2002) Pathology of fetal and neonatal brain development: Identifying the timing. In: Squier W (ed) *Acquired Damage to the Developing Brain: Timing and causation*. Arnold, London, pp 110–127
- Staudt M, Niemann G, Grodd W, Krägeloh-Mann I (2000) The pyramidal tract in congenital hemiparesis: Relationship between morphology and function in periventricular lesions. *Neuropediatrics* 31:257–264
- Stephan H (1975) Allocortex. *Handbuch der mikroskopischen Anatomie des Menschen*, Band 4, Teil 9. Springer, Berlin Heidelberg New York

- Streeter GL (1911) Die Entwicklung des Nervensystems. In: Keibel F, Mall FP (Hrsg) Handbuch der Entwicklungsgeschichte des Menschen, Zweiter Band. Hirzel, Leipzig, pp 1–156
- Streeter GL (1912) The development of the nervous system. In: Keibel F, Mall FP (eds) Manual of Human Embryology, Vol 2. Lippincott, Philadelphia, PA, pp 1–156
- Streeter GL (1915) The development of the venous sinuses in the dura mater in the human embryo. *Am J Anat* 18:145–178
- Streeter GL (1918) The developmental alterations in the vascular system of the brain of the human embryo. *Contrib Embryol Carnegie Instn* 8:5–38
- Streeter GL (1951) Developmental Horizons in Human Embryos. Age groups XI to XXIII. Carnegie Institution of Washington, Washington, DC
- Supèr H, Soriano E, Uylings HBM (1998) The functions of the preplate in development and evolution of the neocortex and hippocampus. *Brain Res Rev* 27:40–64
- Suttner N, Mura J, Tedeschi H, Ferreira MAT, Wen HT, de Oliveira E, Rhoton AL Jr (2000) Persistent trigeminal artery: A unique anatomic specimen—Analysis and therapeutic implications. *Neurosurgery* 47:428–434
- Takashima S, Tanaka K (1978) Development of cerebrovascular architecture and its relationship to periventricular leukomalacia. *Arch Neurol* 35:11–16
- ten Donkelaar HJ (2000) Development and regenerative capacity of descending supraspinal pathways in tetrapods: A comparative approach. *Adv Anat Embryol Cell Biol* 154:1–145
- ten Donkelaar HJ, Lammens M, Wesseling P, Thijssen HOM, Renier WO (2003) Development and developmental disorders of the human cerebellum. *J Neurol* 250:1025–1036
- ten Donkelaar HJ, Lammens M, Wesseling P, Hori A, Keyser A, Rotteveel J (2004) Development and malformations of the human pyramidal tract. *J Neurol* 251:1429–1442
- Tsuboi K, Maki Y, Hori A, Ebihara R (1984) Accessory ventricles of the posterior horn. *Prog Comp Tomogr* 6:529–534
- Van den Bergh R, Vander Eecken H (1968) Anatomy and embryology of cerebral circulation. *Prog Brain Res* 30:1–25
- van der Knaap MS, Valk J (1988) Classification of congenital abnormalities of the CNS. *AJNR Am J Neuroradiol* 9:315–326
- van der Knaap MS, Valk J (1990) MR imaging of the various stages of normal myelination during the first year of life. *Neuroradiology* 31:459–470
- van der Knaap MS, Valk J (1995) Magnetic Resonance of Myelin, Myelination and Myelin Disorders, 2nd ed. Springer, Berlin Heidelberg New York
- van Wezel-Meijler G, van der Knaap MS, Sie LTL, Oosting J, Taets van Amerongen AHM, Cranendonk A, Lafeber HN (1998) Magnetic resonance imaging of the brain in premature infants during the neonatal period. Normal phenomena and reflection of mild ultrasound abnormalities. *Neuropediatrics* 29:89–96
- van Zalen-Sprock RM, van Vugt JMG, van Geijn HPM (1996) First-trimester sonographic detection of neurodevelopmental abnormalities in some single-gene defects. *Prenat Diagn* 16:199–202
- Vieille-Grosjean I, Hunt P, Gulisano M, Boncinelli E, Thorogood P (1997) Branchial HOX gene expression and human craniofacial development. *Dev Biol* 183:49–60
- Volpe JJ (1987) *Neurology of the Newborn*, 2nd ed. Saunders, Philadelphia, PA
- Volpe JJ (1998) Neurologic outcome of prematurity. *Arch Neurol* 55:297–300
- Volpe JJ (2001) Neurobiology of periventricular leukomalacia in the premature infant. *Pediatr Res* 50:553–562
- von Baer KE (1828) Über die Entwicklungsgeschichte der Thiere, Beobachtung und Reflexion. Bornträger, Königsberg
- Wang VY, Zoghbi HY (2001) Genetic regulation of cerebellar development. *Nat Rev Neurosci* 2:484–491
- Wechsler-Reya RJ, Scott MP (1999) Control of neuronal precursor proliferation in the cerebellum by sonic hedgehog. *Neuron* 22:103–114
- Weindling M (2002) Clinical aspects of brain injury of the preterm brain. In: Lagercrantz H, Hanson M, Evrard P, Rodeck CH (eds) *The Newborn Brain – Neuroscience and clinical applications*. Cambridge University Press, Cambridge, pp 443–478
- Wigglesworth JS, Pape KE (1980) Pathophysiology of intracranial haemorrhage in the newborn. *J Perinat Med* 8:119–133
- Wilkie AOM, Morriss-Kay GM (2001) Genetics of craniofacial development and malformation. *Nat Rev Genet* 2:458–468
- Windle WF (1970) Development of neural elements in human embryos of four to seven weeks gestation. *Exp Neurol Suppl* 5:44–83
- Windle WF, Fitzgerald JE (1937) Development of the spinal reflex mechanism in human embryos. *J Comp Neurol* 67:493–509
- Wingate RJT (2001) The rhombic lip and early cerebellar development. *Curr Opin Neurobiol* 11:82–88
- Witters I, Moerman P, Devriendt K, Braet P, Van Schoubroeck D, Van Assche FA, Fryns JP (2002) Two siblings with early onset fetal akinesia deformation sequence and hydranencephaly: Further evidence for autosomal recessive inheritance of hydranencephaly, Fowler type. *Am J Med Genet* 108:41–44
- Wollschlaeger G, Wollschlaeger PB (1964) The primitive trigeminal artery as seen angiographically and at postmortem examination. *AJR Am J Roentgenol* 92:761–768
- Wurst W, Bally-Cuif L (2001) Neural plate patterning: Upstream and downstream of the isthmus organizer. *Nat Rev Neurosci* 2:99–108
- Yakovlev PI, Lecours AR (1967) The myelogenetic cycles of regional maturation of the brain. In: Minkowski A (ed) *Regional Development of the Brain in Early Life*. Blackwell, Oxford, pp 3–70
- Yamadori T (1965) Die Entwicklung des Thalamuskerns mit ihren ersten Fasersystemen bei menschlichen Embryonen. *J Hirnforsch* 7:393–413
- Zecevic N, Milosevic A, Rakic S, Marín-Padilla M (1999) Early development and composition of the human primordial plexiform layer: An immunohistochemical study. *J Comp Neurol* 412:241–254